Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 20 of 26 returned.

☐ 1. Document ID: US 6448032 B1

Using default format because multiple data bases are involved.

L39: Entry 1 of 26 File: USPT Sep 10, 2002

US-PAT-NO: 6448032
DOCUMENT-IDENTIFIER: US 6448032 B1

TITLE: Human melanocyte stimulating hormone receptor polypeptide and DNA

DATE-ISSUED: September 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wikberg; Jarl	S-905 92 Ume.ang.			SE
Chhajlani; Vijay	S-752 42 Uppsala			SE

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.1, 435/320.1, 435/325, 435/69.7, 530/300, 530/306, 530/312, 530/350, 536/23.1, 536/23.4, 536/23.5, 536/24.33

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 2. Document ID: US 6117645 A

L39: Entry 2 of 26 File: USPT Sep 12, 2000

US-PAT-NO: 6117645
DOCUMENT-IDENTIFIER: US 6117645 A

TITLE: Human LH-RH receptor expression cells and use thereof

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 3. Document ID: US 6114139 A

L39: Entry 3 of 26 File: USPT Sep 5, 2000

US-PAT-NO: 6114139
DOCUMENT-IDENTIFIER: US 6114139 A
** See image for Certificate of Correction **

TITLE: G-protein coupled receptor protein and a DNA encoding the receptor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 4. Document ID: US 5972939 A

L39: Entry 4 of 26 File: USPT Oct 26, 1999

US-PAT-NO: 5972939
DOCUMENT-IDENTIFIER: US 5972939 A

TITLE: Cyclopentene derivatives useful as antagonists of the motilin receptor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 5. Document ID: US 5912235 A

L39: Entry 5 of 26 File: USPT Jun 15, 1999

US-PAT-NO: 5912235
DOCUMENT-IDENTIFIER: US 5912235 A

TITLE: 10, 13, 15-trioxatricyclo [9.2.1.1..sup.9.6]-pentadecan one derivatives, method for their production and pharmaceutical compositions containing them

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 6. Document ID: US 5734012 A

L39: Entry 6 of 26 File: USPT Mar 31, 1998

US-PAT-NO: 5734012
DOCUMENT-IDENTIFIER: US 5734012 A

TITLE: Cyclic motilin-like polypeptides with gastrointestinal motor stimulating activity

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 7. Document ID: US 5712253 A

L39: Entry 7 of 26 File: USPT Jan 27, 1998

US-PAT-NO: 5712253
DOCUMENT-IDENTIFIER: US 5712253 A
**** See image for Certificate of Correction ****

TITLE: Macrocyclic 13-membered ring derivatives of erythromycins A and B

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 8. Document ID: US 5677184 A

L39: Entry 8 of 26 File: USPT Oct 14, 1997

US-PAT-NO: 5677184
DOCUMENT-IDENTIFIER: US 5677184 A

TITLE: CHO cells that express human LH-RH receptor

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 9. Document ID: US 5658888 A

L39: Entry 9 of 26 File: USPT Aug 19, 1997

US-PAT-NO: 5658888
DOCUMENT-IDENTIFIER: US 5658888 A

TITLE: Erythromycin derivatives

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 10. Document ID: US 5470830 A

L39: Entry 10 of 26 File: USPT Nov 28, 1995

US-PAT-NO: 5470830
DOCUMENT-IDENTIFIER: US 5470830 A

TITLE: Motilin-like polypeptides that inhibit gastrointestinal motor activity

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 11. Document ID: US 5459049 A

L39: Entry 11 of 26 File: USPT Oct 17, 1995

US-PAT-NO: 5459049
DOCUMENT-IDENTIFIER: US 5459049 A
**** See image for Certificate of Correction ****

TITLE: Motilin-like polypeptide and use thereof

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 12. Document ID: US 5432261 A

L39: Entry 12 of 26 File: USPT Jul 11, 1995

US-PAT-NO: 5432261
DOCUMENT-IDENTIFIER: US 5432261 A

TITLE: Motlin-like polypeptide and use thereof

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 13. Document ID: US 5422341 A

L39: Entry 13 of 26 File: USPT Jun 6, 1995

US-PAT-NO: 5422341
DOCUMENT-IDENTIFIER: US 5422341 A

TITLE: Motilin-like polypeptides with gastrointestinal motor stimulating activity

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 14. Document ID: US 5418224 A

L39: Entry 14 of 26 File: USPT May 23, 1995

US-PAT-NO: 5418224
DOCUMENT-IDENTIFIER: US 5418224 A

TITLE: 4,13-dioxabicyclo[8.2.1]tridecenone compounds and pharmaceutical compositions containing them

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

---

☐ 15. Document ID: JP 2000044595 A

L39: Entry 15 of 26 File: JPAB Feb 15, 2000

PUB-NO: JP02000044595A
DOCUMENT-IDENTIFIER: JP 2000044595 A
TITLE: PHENETHYLAMINE DERIVATIVE

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 16. Document ID: JP 09249620 A

L39: Entry 16 of 26 File: JPAB Sep 22, 1997

PUB-NO: JP409249620A
DOCUMENT-IDENTIFIER: JP 09249620 A

TITLE: ARYLALKANE DERIVATIVE

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 17. Document ID: EP 1006122 A1

L39: Entry 17 of 26 File: EPAB Jun 7, 2000

PUB-NO: EP001006122A1
DOCUMENT-IDENTIFIER: EP 1006122 A1
TITLE: PHENETHYLAMINE DERIVATIVES

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 18. Document ID: WO 9921846 A1

L39: Entry 18 of 26 File: EPAB May 6, 1999

PUB-NO: WO009921846A1
DOCUMENT-IDENTIFIER: WO 9921846 A1
TITLE: CYCLOPENTENE DERIVATIVES USEFUL AS ANTAGONISTS OF THE MOTILIN RECEPTOR

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 19. Document ID: WO 9909053 A1

L39: Entry 19 of 26 File: EPAB Feb 25, 1999

PUB-NO: WO009909053A1
DOCUMENT-IDENTIFIER: WO 9909053 A1
TITLE: PHENETHYLAMINE DERIVATIVES

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 20. Document ID: US 6677430 B1

L39: Entry 20 of 26 File: DWPI Jan 13, 2004

DERWENT-ACC-NO: 2004-068645
DERWENT-WEEK: 200407
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TITLE: Novel fluorescent peptide compound, useful for imaging cell receptor sites, cell sorting and flow cytometry

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Term	Documents
@AY	22467584
(11 AND (@AY < "1999")).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	26
(L11 AND @AY<1999).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	26

Display Format: - Change Format

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Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 21 through 26 of 26 returned.

☐ 21. Document ID: WO 200024907 A2, AU 200014477 A, EP 1124968 A2, US 6403775 B1, JP 2002528467 W

Using default format because multiple data bases are involved.

L39: Entry 21 of 26 File: DWPI May 4, 2000

DERWENT-ACC-NO: 2000-365118
DERWENT-WEEK: 200382
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: New polyketide compounds, useful as agents having antibiotic and antiparasitic activity or for treating e.g. gastric disorders, gall bladder disorders or diabetics with autonomic neuropathy

INVENTOR: MCDANIEL, R

PRIORITY-DATA: 1998US-105987P (October 28, 1998), 1999US-0429349 (October 28, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200024907 A2	May 4, 2000	E	036	C12N015/52
AU 200014477 A	May 15, 2000		000	
EP 1124968 A2	August 22, 2001	E	000	C12N015/52
US 6403775 B1	June 11, 2002		000	C07H017/08
JP 2002528467 W	September 3, 2002		056	C07D313/00

INT-CL (IPC): A61 P 1/00; A61 P 29/00; A61 P 31/00; C07 D 313/00; C07 D 321/00; C07 H 17/08; C12 N 1/21; C12 N 9/10; C12 N 15/09; C12 N 15/52; C12 N 15/62; C12 P 19/62; C12 N 1/21; C12 N 1/21; C12 N 1/21; C12 N 1/21; C12 N 1/21; C12 N 1/21; C12 R 1:01; C12 R 1:29; C12 R 1:465; C12 R 1:48; C12 R 1:54; C12 R 1:61

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 22. Document ID: HU 222539 B1, DE 19805822 A1, EP 937734 A1, NO 9900675 A, CZ 9900458 A3, AU 9916438 A, HU 9900263 A2, ZA 9900678 A, JP 11269193 A, CA 2260315 A1, SK 9900150 A3, CN 1239718 A, BR 9900442 A, NZ 334087 A, KR 99072345 A, US 6165985 A, MX 9901491 A1, IL 128238 A, NO 310917 B1, AU 748670 B

L39: Entry 22 of 26 File: DWPI Aug 28, 2003

DERWENT-ACC-NO: 1999-509364
DERWENT-WEEK: 200363
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TITLE: New contracted ring derivatives of erythromycin A which do not have antibiotic activity and are useful in treatment of motility disorders

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

---

☐ 23. Document ID: NO 316118 B1, WO 9921846 A1, AU 9912024 A, US 5972939 A, EP 1027342 A1, NO 200002036 A, ZA 9809784 A, BR 9813169 A, CZ 200001447 A3, SK 200000606 A3, CN 1278255 A, HU 200004851 A2, KR 2001031569 A, AU 738370 B, JP 2001521030 W, TW 466225 A, MX 2000004133 A1

L39: Entry 23 of 26 File: DWPI Dec 15, 2003

DERWENT-ACC-NO: 1999-312927
DERWENT-WEEK: 200382
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TITLE: New cyclopentene derivatives useful in treating gastrointestinal disorders associated with antagonising the motilin receptor, including e.g. irritable bowel syndrome

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 24. Document ID: WO 9909053 A1, TW 460478 A, AU 9886490 A, JP 2000044595 A, EP 1006122 A1, CN 1272114 A, US 6255285 B1, KR 2001022924 A, AU 741216 B

L39: Entry 24 of 26 File: DWPI Feb 25, 1999

DERWENT-ACC-NO: 1999-180967
DERWENT-WEEK: 200248
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TITLE: New phenethylamine derivatives are motilin receptor antagonists - for treating e.g. Crohn's disease, pancreatitis, diabetes and obesity

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 25. Document ID: HU 222540 B1, EP 838469 A1, DE 19644195 A1, NO 9704934 A, SK 9701419 A3, AU 9742788 A, CZ 9703106 A3, JP 10130297 A, ZA 9709059 A, CA 2219311 A, HU 9701660 A2, NZ 328979 A, US 5912235 A, KR 98032626 A, MX 9707974 A1, BR 9705157 A, IL 121969 A, NO 308362 B1, AU 726092 B, BR 9705143 A, EP 838469 B1, DE 59705964 G, MX 199461 B, RU 2181727 C2, ES 2170318 T3, SK 283114 B6, TW 489088 A, CN 1186808 A, CZ 291768 B6, PH 1199758268 B1

L39: Entry 25 of 26 File: DWPI Aug 28, 2003

DERWENT-ACC-NO: 1998-232593
DERWENT-WEEK: 200363
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TITLE: New hexa:methyl-10,13,15-tri:oxa-tri:cyclo-penta:decanone derivatives - useful as motilin receptor agonists in treatment of e.g. dyspepsia, gastric reflux

and postoperative gastric motility disorders

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 26. Document ID: JP 09249620 A

L39: Entry 26 of 26 File: DWPI Sep 22, 1997

DERWENT-ACC-NO: 1998-002784
DERWENT-WEEK: 199801

TITLE: New aminophenyl- or amino:cyclohexyl-phenyl:alkane derivatives - used as motilin receptor stimulants, prepared e.g. by Wittig reaction

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Term	Documents
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(11 AND (@AY < "1999")).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	26
(L11 AND @AY<1999).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	26

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Refine Search

Search Results -

Term	Documents
LIGAND	96493
LIGANDS	68557
TRANSFECT$6	0
TRANSFECT	10739
TRANSFECTABLE	373
TRANSFECTABLES	1
TRANSFECTABLY	1
TRANSFECTACE	388
"TRANSFECTACE.TM"	4
TRANSFECTACON	2
TRANSFECTACONS	2
(L40 AND (LIGAND WITH TRANSFECT$6)).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	0

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US Patents Full-Text Database
US OCR Full-Text Database
EPO Abstracts Database
JPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L42

Refine Search

Recall Text Clear Interrupt

Search History

DATE: Sunday, February 08, 2004 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
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L39	L11 and @ay<1999	26	L39
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L37	L11 and 1991.ay.	0	L37
L36	L11 and 1992.ay.	2	L36
L35	L11 and 1993.ay.	3	L35
L34	L11 and 1994.ay.	1	L34
L33	L11 and 1995.ay.	4	L33
L32	L11 and 1996.ay.	6	L32
L31	L11 and 1999.ay.	14	L31
L30	L11 and 1998.ay.	9	L30
L29	L11 and 1997.ay.	4	L29
L28	L11 and 1987.ay.	0	L28
L27	L12 and 2003.ay.	0	L27
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L14	L11 and @ad<1999	0	L14
L13	L11 and @ad<1998	0	L13
L12	L11 and @py<1997	5	L12
L11	motilin receptor	106	L11
L10	L9 and motilin	2	L10
L9	macneil.in.	334	L9
L8	L7 and motilin	0	L8
L7	smith-roy.in.	27	L7
L6	L5 and motilin	2	L6
L5	pong.in.	516	L5
L4	sheng shung.in.	3	L4
L3	sheng-shung-pong.in.	0	L3
L2	sheng-sheng-pong.in.	0	L2

L1	Macneil-andrew-howard.in.	0	L1

END OF SEARCH HISTORY

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FILE 'HOME' ENTERED AT 22:55:44 ON 08 FEB 2004

=> FIL STNGUIDE
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Feb  6, 2004 (20040206/UP).

=> file .bio
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.06       0.27

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=> s motilin receptor#
L1          892 MOTILIN RECEPTOR#

=> s l1 and range=(1990-1998)
MISSING TERM AFTER L1 AND
Operators must be followed by a search term, L-number, or query name.

=> s l1 range=(1990-1998)
'(1990-1998)' IS NOT A VALID RANGE FOR FILE 'MEDLINE'
Valid RANGE values are file specific.  For more information, enter
HELP RANGE or HELP SET RANGE at an arrow prompt (=>) in the current
file.
ENTER RANGE FOR FILE 'MEDLINE' OR (ALL):end
SEARCH ENDED BY USER
   1 FILES SEARCHED...
L2          376 L1

=> s l1 and 1990
L3            0 L1 AND 1990

=> s l1 and 1991
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=> s l1 and 1998
L7            5 L1 AND 1998

=> s l1 and 1994
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=> s l1 and 1996
L10           1 L1 AND 1996

=> s l1 and 1997
L11           6 L1 AND 1997

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=> s l1 and 2003
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=> s l1 and 2004
L18           0 L1 AND 2004

=> l8 d ibib abs
MISSING OPERATOR L8 D IBIB
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l8 ibib abs

L8   ANSWER 1 OF 3     MEDLINE on STN
ACCESSION NUMBER:    95328382     MEDLINE
DOCUMENT NUMBER:     95328382   PubMed ID: 7604665
TITLE:               Georges Brohee Prize 1994. Motilin and the
                     enteric nervous system in the control of interdigestive and
                     postprandial gastric motility.
AUTHOR:              Tack J
CORPORATE SOURCE:    Centre for Gastroenterological Research, University
                     Hospital Gasthuisberg, Catholic University of Leuven.
SOURCE:              ACTA GASTROENTEROLOGICA BELGICA, (1995 Jan-Feb) 58 (1)
                     21-30.  Ref: 38
                     Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY:        Belgium
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
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General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950822
Last Updated on STN: 19950822
Entered Medline: 19950809

AB The upper gastrointestinal tract displays two different functional states: the interdigestive or fasting state, and the fed state. The fasting state is characterized by a cyclical motor pattern, the migrating motor complex (MMC). The control of the MMC is incompletely understood. Plasma levels of the hormone motilin fluctuate in synchrony with MMC, but it is still controversial whether a motilin peak triggers the MMC or whether the MMC causes motilin release. We used the motilin agonistic properties of erythromycin to resolve this issue in man. Administration of a low dose of erythromycin induced a MMC which started from the gastric antrum, unaccompanied by a motilin peak. This finding argues against a release of motilin secondary to the MMC and supports our hypothesis that in man motilin peaks trigger the MMC. We observed that higher doses of erythromycin no longer induced a MMC, but stimulated antral contractility. The enteric nervous system is involved in the control of both the fasting and fed state at each level of the gastrointestinal tract. We hypothesized that the target for motilin to trigger the MMC is the enteric nervous system in the gastric antrum. Yet, no physiological data on antral enteric neurons were available. We performed the first electrophysiological study of myenteric neurons of the gastric antrum, revealing unique electrical and synaptic properties in comparison to other regions of the gastrointestinal tract. We confirmed the role of the enteric nervous system of the gastric antrum in the control of the MMC by directly demonstrating the presence of **motilin receptors** on a subpopulation of neurons. We demonstrated that endogenous and exogenous substances that stimulate (cholecystokinin, cisapride, erythromycin) or inhibit (norepinephrine, 5-hydroxytryptamine) gastric emptying all act on antral enteric neurons. These observations strongly support the hypothesis that the enteric nervous system in the gastric antrum plays a key role in the coordination of antral peristalsis and the regulation of gastric emptying. Finally, we hypothesized that the actions of erythromycin on **motilin receptors** on enteric neurons and intestinal smooth muscle offer a potential for therapeutic applications in gastrointestinal motility disorders. We confirmed this by demonstrating gastrointestinal motility stimulating activity of erythromycin in patients with diabetic gastroparesis.

=> d his

(FILE 'HOME' ENTERED AT 22:55:44 ON 08 FEB 2004)

FILE 'STNGUIDE' ENTERED AT 22:56:00 ON 08 FEB 2004

FILE 'MEDLINE, JAPIO, BIOSIS, SCISEARCH, WPIDS, CAPLUS, EMBASE' ENTERED AT 22:56:15 ON 08 FEB 2004

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L4 0 S L1 AND 1991
L5 0 S L1 AND 1992
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L8 3 S L1 AND 1994
L9 0 S L1 AND 1995
L10 1 S L1 AND 1996
L11 6 S L1 AND 1997
L12 5 S L1 AND 1998

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L17             2 S L1 AND 2003
L18             0 S L1 AND 2004

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L19           391 DUP REM L1 (501 DUPLICATES REMOVED)

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L20             1 L19 AND VECTOR# AND LIGAND#

=> l1 and ligand and (transfected or transfecting or transfect)
L21           10 L1 AND LIGAND AND (TRANSFECTED OR TRANSFECTING OR TRANSFECT)

=> d l20 ibib abs

L20  ANSWER 1 OF 1  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER:     2000-105868 [09]   WPIDS
DOC. NO. CPI:         C2000-031800
TITLE:                Novel receptor protein for screening compounds used in
                      treating irritable bowel syndrome, constipation and other
                      gastric conditions.
DERWENT CLASS:        B04 D16
INVENTOR(S):          FEIGHNER, S D; HOWARD, A D; MACNEIL, D; MCKEE, K;
                      PATCHETT, A A; PONG, S; SMITH, R G; TAN, C
PATENT ASSIGNEE(S):   (MERI) MERCK & CO INC
COUNTRY COUNT:        22
PATENT INFORMATION:

     PATENT NO   KIND DATE     WEEK      LA   PG
     ---------------------------------------------
     WO 9964436    A1 19991216 (200009)* EN   35
        RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
         W: CA JP US
     EP 1086117    A1 20010328 (200118)  EN
         R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
     JP 2002517507 W  20020618 (200242)       42

APPLICATION DETAILS:

     PATENT NO   KIND                  APPLICATION      DATE
     ------------------------------------------------------------
     WO 9964436    A1                  WO 1999-US12773  19990608
     EP 1086117    A1                  EP 1999-928453   19990608
                                       WO 1999-US12773  19990608
     JP 2002517507 W                   WO 1999-US12773  19990608
                                       JP 2000-553444   19990608

FILING DETAILS:

     PATENT NO   KIND                  PATENT NO
     ---------------------------------------------
     EP 1086117    A1 Based on         WO 9964436
     JP 2002517507 W  Based on         WO 9964436

PRIORITY APPLN. INFO: US 1998-89098P   19980612
AN   2000-105868 [09]   WPIDS
AB   WO   9964436 A UPAB: 20000218
     NOVELTY - A motilin receptor (I) MTL-R1 (GPR 38) which
     is substantially free from receptor associated proteins, is new.
          DETAILED DESCRIPTION - An INDEPENDENT CLAIM  is also included for a
     method of determining binding of a ligand (II) to (I)
```

comprising:

(a) transfecting test cells with an expression **vector** encoding (I);

(b) exposing them to (II);

(c) measuring amount of binding of (II) to (I); and

(d) comparing this level to that of the amount of binding of (II) to control cells that have not been transfected with (I), a greater level of binding in the test cells compared determines that (II) is capable of binding (I).

ACTIVITY - Dermatological; antidiabetic; laxative; litholytic; antiinflammatory; antidiarrheic.

MECHANISM OF ACTION - Stimulator or inhibitor of **motilin receptor.**

USE - (I) is used to identify its agonists and antagonists which can be used for treating gastric motility disorders, functional defects, disorders secondary to neurological disorders e.g. scleroderma, paraneoplastic syndromes radiation induced dysmotility, diabetes, infections, stress-related motility disorders, psychgenic disorders, gastroparesis, gastro-esophageal reflux disease, constipation, chronic idiopathis pseudo obstruction, acute fecal impaction, postoperative ileus, gallstones, infantile collic, irritable bowel syndrome, non-ulcer dyspepsion, non-cardiac chest pain and diarrhea. They can also be used in the preparation for colonoscopy, endoscopy and duodenal intubation. Nucleic acid encoding (I) or its functional variants can be used as DNA probes to identify **motilin receptor** from other species.

ADVANTAGE - (I) enables the identification of safe and selective **motilin receptor** agonists.

Dwg.0/11

=> d l21 ibib abs 1-10

L21 ANSWER 1 OF 10 MEDLINE on STN

ACCESSION NUMBER: 2003514700 IN-PROCESS

DOCUMENT NUMBER: PubMed ID: 12907757

TITLE: High constitutive signaling of the ghrelin receptor--identification of a potent inverse agonist.

AUTHOR: Holst Birgitte; Cygankiewicz Adam; Jensen Tine Halkjaer; Ankersen Michael; Schwartz Thue W

CORPORATE SOURCE: Laboratory for Molecular Pharmacology, Institute of Pharmacology, The Panum Institute, University of Copenhagen, DK-2200 Copenhagen, Denmark.. b.holst@molpharm.dk

SOURCE: Molecular endocrinology (Baltimore, Md.), (2003 Nov) 17 (11) 2201-10.
Journal code: 8801431. ISSN: 0888-8809.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20031101
Last Updated on STN: 20031219

AB Ghrelin is a GH-releasing peptide that also has an important role as an orexigenic hormone-stimulating food intake. By measuring inositol phosphate turnover or by using a reporter assay for transcriptional activity controlled by cAMP-responsive elements, the ghrelin receptor showed strong, **ligand**-independent signaling in **transfected** COS-7 or human embryonic kidney 293 cells. Ghrelin and a number of the known nonpeptide GH secretagogues acted as agonists stimulating inositol phosphate turnover further. In contrast, the low potency ghrelin antagonist, [D-Arg1,D-Phe5,D-Trp7,9,Leu11]-substance P was surprisingly found to be a high potency (EC50 = 5.2 nm) full inverse agonist as it decreased the constitutive signaling of the ghrelin receptor down to that observed in untransfected cells. The homologous

motilin receptor functioned as a negative control as it did not display any sign of constitutive activity; however, upon agonist stimulation the **motilin receptor** signaled as strongly as the unstimulated ghrelin receptor. It is concluded that the ghrelin receptor is highly constitutively active and that this activity could be of physiological importance in its role as a regulator of both GH secretion and appetite control. It is suggested that inverse agonists for the ghrelin receptor could be particularly interesting for the treatment of obesity.

L21 ANSWER 2 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2003508897 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 14504130
TITLE: The rabbit **motilin receptor**: molecular characterisation and pharmacology.
AUTHOR: Dass N B; Hill J; Muir A; Testa T; Wise A; Sanger G J
CORPORATE SOURCE: Department of Gastrointestinal Research, Neurology and Gastroenterology Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK.. nin_2_dass@gsk.com
SOURCE: British journal of pharmacology, (2003 Nov) 140 (5) 948-54. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031031
Last Updated on STN: 20031219

AB Following identification of the human **motilin receptor**, we isolated the rabbit orthologue by PCR amplification and found this to be 85% identical to the open reading frame of the human receptor. The protein encoded was 84% identical to the human polypeptide. In HEK293T cells **transfected** with the rabbit receptor, motilin concentration-dependently increased intracellular calcium mobilisation (pEC50=9.25). After transfection with Go1alpha, motilin similarly stimulated [35S]GTPgammaS binding (pEC50=8.87). Using both systems, similar values were obtained with the human receptor, with rank-order potencies of motilin=[Nle13]-motilin>erythromycin; ghrelin was ineffective. In circular muscle preparations of rabbit gastric antrum, [Nle13]-motilin 0.1-30 nM concentration-dependently increased the amplitude of electrically-evoked, neuronally-mediated contractions (pEC50=8.3); higher concentrations increased the muscle tension (30-3000 nM). Both responses to [Nle13]-motilin faded rapidly during its continual presence. Rat or human ghrelin 0.01-10 microM were without activity. Erythromycin 30-3000 nM and 10 microM, respectively, increased neuronal activity and muscle tension in rabbit stomach. Unlike [Nle13]-motilin, the increase in neuronal activity did not fade during continual presence of submaximally-effective concentrations of erythromycin; some fade was observed at higher concentrations. We conclude that the pharmacology of the rabbit **motilin receptor** is similar to the human orthologue and, when expressed as a recombinant, comparable to the native receptor. However, in terms of their ability to increase neuronal activity in rabbit stomach, [Nle13]-motilin and erythromycin are distinguished by different response kinetics, reflecting different rates of **ligand** degradation and/or interaction with the receptor.

L21 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:561164 BIOSIS
DOCUMENT NUMBER: PREV200300550439
TITLE: High constitutive signaling of the ghrelin receptor: Identification of a potent inverse agonist.
AUTHOR(S): Holst, Birgitte [Reprint Author]; Cygankiewicz, Adam; Jensen, Tine Halkjaer; Ankersen, Michael; Schwartz, Thue W.
CORPORATE SOURCE: Laboratory for Molecular Pharmacology, Institute of Pharmacology, Panum Institute, University of Copenhagen,

Blegdamsvej 3, DK-2200, Copenhagen, Denmark
b.holst@molpharm.dk
SOURCE: Molecular Endocrinology, (November 2003) Vol. 17, No. 11, pp. 2201-2210. print.
ISSN: 0888-8809 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Nov 2003
Last Updated on STN: 26 Nov 2003
AB Ghrelin is a GH-releasing peptide that also has an important role as an orexigenic hormone-stimulating food intake. By measuring inositol phosphate turnover or by using a reporter assay for transcriptional activity controlled by cAMP-responsive elements, the ghrelin receptor showed strong, **ligand**-independent signaling in **transfected** COS-7 or human embryonic kidney 293 cells. Ghrelin and a number of the known nonpeptide GH secretagogues acted as agonists stimulating inositol phosphate turnover further. In contrast, the low potency ghrelin antagonist, (D-Arg1,D-Phe5,D-Trp7,9,Leu11)-substance P was surprisingly found to be a high potency (EC50=5.2 nM) full inverse agonist as it decreased the constitutive signaling of the ghrelin receptor down to that observed in untransfected cells. The homologous **motilin receptor** functioned as a negative control as it did not display any sign of constitutive activity; however, upon agonist stimulation the **motilin receptor** signaled as strongly as the unstimulated ghrelin receptor. It is concluded that the ghrelin receptor is highly constitutively active and that this activity could be of physiological importance in its role as a regulator of both GH secretion and appetite control. It is suggested that inverse agonists for the ghrelin receptor could be particularly interesting for the treatment of obesity.

L21 ANSWER 4 OF 10 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:966398 SCISEARCH
THE GENUINE ARTICLE: 738EL
TITLE: High constitutive signaling of the ghrelin receptor - Identification of a potent inverse agonist
AUTHOR: Holst B (Reprint); Cygankiewicz A; Jensen T H; Ankersen M; Schwartz T W
CORPORATE SOURCE: Univ Copenhagen, Panum Inst, Mol Pharmacol Lab, Inst Pharmacol, Blegdamsvej 3, DK-2000 Copenhagen, Denmark (Reprint); Univ Copenhagen, Panum Inst, Mol Pharmacol Lab, Inst Pharmacol, DK-2000 Copenhagen, Denmark; 7TM Pharma AS, DK-2970 Horsholm, Denmark; Novo Nordisk AS, Dept Med Chem, DK-2760 Malov, Denmark
COUNTRY OF AUTHOR: Denmark
SOURCE: MOLECULAR ENDOCRINOLOGY, (1 NOV 2003) Vol. 17, No. 11, pp. 2201-2210.
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110 USA.
ISSN: 0888-8809.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Ghrelin is a GH-releasing peptide that also has an important role as an orexigenic hormone-stimulating food intake. By measuring inositol phosphate turnover or by using a reporter assay for transcriptional activity controlled by cAMP-responsive elements, the ghrelin receptor showed strong, **ligand**-independent signaling in **transfected** COS-7 or human embryonic kidney 293 cells. Ghrelin and a number of the known nonpeptide GH secretagogues acted as agonists stimulating inositol phosphate turnover further. In contrast, the low potency ghrelin antagonist, [D-Arg(1), D-Phe(5), D-Trp(7,9), Leu(11)]-substance P was surprisingly found to be a high potency (EC50 = 5.2 nM) full inverse agonist as it decreased the constitutive signaling of the

ghrelin receptor down to that observed in untransfected cells. The homologous **motilin receptor** functioned as a negative control as it did not display any sign of constitutive activity; however, upon agonist stimulation the **motilin receptor** signaled as strongly as the unstimulated ghrelin receptor. It is concluded that the ghrelin receptor is highly constitutively active and that this activity could be of physiological importance in its role as a regulator of both GH secretion and appetite control. It is suggested that inverse agonists for the ghrelin receptor could be particularly interesting for the treatment of obesity.

L21 ANSWER 5 OF 10 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:950945 SCISEARCH
THE GENUINE ARTICLE: 737PK
TITLE: The rabbit **motilin receptor**: molecular characterisation and pharmacology
AUTHOR: Dass N B (Reprint); Hill J; Muir A; Testa T; Wise A; Sanger G J
CORPORATE SOURCE: GlaxoSmithKline, Dept Gastrointestinal Res Neurol & Gastroenterol, Ctr Excellence Drug Discovery, New Frontiers Sci Pk, 3rd Ave, Harlow CM19 5AW, Essex, England (Reprint); GlaxoSmithKline, Dept Gastrointestinal Res Neurol & Gastroenterol, Ctr Excellence Drug Discovery, Harlow CM19 5AW, Essex, England; GlaxoSmithKline, Discovery Res, Harlow CM19 5AW, Essex, England
COUNTRY OF AUTHOR: England
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (NOV 2003) Vol. 140, No. 5, pp. 948-954.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.
ISSN: 0007-1188.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 24

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 1 Following identification of the human **motilin receptor**, we isolated the rabbit orthologue by PCR amplification and found this to be 85% identical to the open reading frame of the human receptor. The protein encoded was 84% identical to the human polypeptide.

2 In HEK293T cells **transfected** with the rabbit receptor, motilin concentration-dependently increased intracellular calcium mobilisation (pEC(50) = 9.25). After transfection with G(o1)alpha, motilin similarly stimulated [S-35]GTPgammaS binding (pEC(50) = 8.87). Using both systems, similar values were obtained with the human receptor, with rank-order potencies of motilin =[Nle(13)]-motilin > erythromycin; ghrelin was ineffective.

3 In circular muscle preparations of rabbit gastric antrum, [Nle(13)]-motilin 0.1-30 nM concentration-dependently increased the amplitude of electrically-evoked, neuronally-mediated contractions (pEC(50) = 8.3); higher concentrations increased the muscle tension (30-3000 nM). Both responses to [Nle(13)]-motilin faded rapidly during its continual presence. Rat or human ghrelin 0.01-10 muM were without activity.

4 Erythromycin 30-3000 nM and 10 muM, respectively, increased neuronal activity and muscle tension in rabbit stomach. Unlike [Nle(13)]-motilin, the increase in neuronal activity did not fade during continual presence of submaximally-effective concentrations of erythromycin; some fade was observed at higher concentrations.

5 We conclude that the pharmacology of the rabbit **motilin receptor** is similar to the human orthologue and, when expressed as a recombinant, comparable to the native receptor. However, in terms of their ability to increase neuronal activity in rabbit stomach, [Nle(13)]-motilin and erythromycin are distinguished by different response kinetics, reflecting different rates of **ligand** degradation and/or interaction with the receptor.

L21 ANSWER 6 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-105868 [09] WPIDS
DOC. NO. CPI: C2000-031800
TITLE: Novel receptor protein for screening compounds used in treating irritable bowel syndrome, constipation and other gastric conditions.
DERWENT CLASS: B04 D16
INVENTOR(S): FEIGHNER, S D; HOWARD, A D; MACNEIL, D; MCKEE, K; PATCHETT, A A; PONG, S; SMITH, R G; TAN, C
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9964436	A1	19991216	(200009)*	EN	35
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
EP 1086117	A1	20010328	(200118)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
JP 2002517507 W		20020618	(200242)		42

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9964436	A1	WO 1999-US12773	19990608
EP 1086117	A1	EP 1999-928453	19990608
		WO 1999-US12773	19990608
JP 2002517507 W		WO 1999-US12773	19990608
		JP 2000-553444	19990608

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1086117	A1 Based on	WO 9964436
JP 2002517507 W	Based on	WO 9964436

PRIORITY APPLN. INFO: US 1998-89098P 19980612
AN 2000-105868 [09] WPIDS
AB WO 9964436 A UPAB: 20000218
NOVELTY - A **motilin receptor** (I) MTL-R1 (GPR 38) which is substantially free from receptor associated proteins, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of determining binding of a **ligand** (II) to (I) comprising:

(a) **transfecting** test cells with an expression vector encoding (I);

(b) exposing them to (II);

(c) measuring amount of binding of (II) to (I); and

(d) comparing this level to that of the amount of binding of (II) to control cells that have not been **transfected** with (I), a greater level of binding in the test cells compared determines that (II) is capable of binding (I).

ACTIVITY - Dermatological; antidiabetic; laxative; litholytic; antiinflammatory; antidiarrheic.

MECHANISM OF ACTION - Stimulator or inhibitor of **motilin receptor.**

USE - (I) is used to identify its agonists and antagonists which can be used for treating gastric motility disorders, functional defects, disorders secondary to neurological disorders e.g. scleroderma, paraneoplastic syndromes radiation induced dysmotility, diabetes, infections, stress-related motility disorders, psychgenic disorders,

gastroparesis, gastro-esophageal reflux disease, constipation, chronic idiopathis pseudo obstruction, acute fecal impaction, postoperative ileus, gallstones, infantile collic, irritable bowel syndrome, non-ulcer dyspepsion, non-cardiac chest pain and diarrhea. They can also be used in the preparation for colonoscopy, endoscopy and duodenal intubation. Nucleic acid encoding (I) or its functional variants can be used as DNA probes to identify **motilin receptor** from other species.

ADVANTAGE - (I) enables the identification of safe and selective **motilin receptor** agonists.

Dwg.0/11

L21 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:963718 CAPLUS

TITLE: The rabbit **motilin receptor**: Molecular characterisation and pharmacology

AUTHOR(S): Dass, N. B.; Hill, J.; Muir, A.; Testa, T.; Wise, A.; Sanger, G. J.

CORPORATE SOURCE: Department of Gastrointestinal Research, Neurology and Gastroenterology Centre of Excellence for Drug Discovery, GlaxoSmithKline, Essex, CM19 5AW, UK

SOURCE: British Journal of Pharmacology (2003), 140(5), 948-954
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1 Following identification of the human **motilin receptor**, we isolated the rabbit orthologue by PCR amplification and found this to be 85% identical to the open reading frame of the human receptor. The protein encoded was 84% identical to the human polypeptide. 2 In HEK293T cells **transfected** with the rabbit receptor, motilin concentration-dependently increased intracellular calcium mobilisation (pEC50 = 9.25). After transfection with Go1α, motilin similarly stimulated [35S]GTPγS binding (pEC50 = 8.87). Using both systems, similar values were obtained with the human receptor, with rank-order potencies of motilin = [Nle13]-motilin > erythromycin; ghrelin was ineffective. 3 In circular muscle prepns. of rabbit gastric antrum, [Nle13]-motilin 0.1-30 nM concentration-dependently increased the amplitude of elec.-evoked, neuronally-mediated contractions (pEC50 = 8.3); higher concns. increased the muscle tension (30-3000 nM). Both responses to [Nle13]-motilin faded rapidly during its continual presence. Rat or human ghrelin 0.01-10 μM were without activity. 4 Erythromycin 30-3000 nM and 10 μM, resp., increased neuronal activity and muscle tension in rabbit stomach. Unlike [Nle13]-motilin, the increase in neuronal activity did not fade during continual presence of submaximally-effective concns. of erythromycin; some fade was observed at higher concns. 5 We conclude that the pharmacol. of the rabbit **motilin receptor** is similar to the human orthologue and, when expressed as a recombinant, comparable to the native receptor. However, in terms of their ability to increase neuronal activity in rabbit stomach, [Nle13]-motilin and erythromycin are distinguished by different response kinetics, reflecting different rates of **ligand** degradation and/or interaction with the receptor.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:876379 CAPLUS

TITLE: High constitutive signaling of the ghrelin receptor-identification of a potent inverse agonist

AUTHOR(S): Holst, Birgitte; Cygankiewicz, Adam; Jensen, Tine Halkjaer; Ankersen, Michael; Schwartz, Thue W.

CORPORATE SOURCE: Laboratory for Molecular Pharmacology, The Panum Institute, University of Copenhagen, Copenhagen, DK-2200, Den.

SOURCE: Molecular Endocrinology (2003), 17(11), 2201-2210
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ghrelin is a GH-releasing peptide that also has an important role as an orexigenic hormone-stimulating food intake. By measuring inositol phosphate turnover or by using a reporter assay for transcriptional activity controlled by cAMP-responsive elements, the ghrelin receptor showed strong, **ligand**-independent signaling in **transfected** COS-7 or human embryonic kidney 293 cells. Ghrelin and a number of the known nonpeptide GH secretagogues acted as agonists stimulating inositol phosphate turnover further. In contrast, the low potency ghrelin antagonist, [D-Arg1,D-Phe5,D-Trp7,9,Leu11]-substance P was surprisingly found to be a high potency (EC50 = 5.2 nM) full inverse agonist as it decreased the constitutive signaling of the ghrelin receptor down to that observed in untransfected cells. The homologous **motilin receptor** functioned as a neg. control as it did not display any sign of constitutive activity; however, upon agonist stimulation the **motilin receptor** signaled as strongly as the unstimulated ghrelin receptor. It is concluded that the ghrelin receptor is highly constitutively active and that this activity could be of physiol. importance in its role as a regulator of both GH secretion and appetite control. It is suggested that inverse agonists for the ghrelin receptor could be particularly interesting for the treatment of obesity.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 9 OF 10 EMBASE
on STN

ACCESSION NUMBER: 2003485756 EMBASE
TITLE: The rabbit **motilin receptor**: Molecular characterisation and pharmacology.
AUTHOR: Dass N.B.; Hill J.; Muir A.; Testa T.; Wise A.; Sanger G.-J.
CORPORATE SOURCE: N.B. Dass, Dept. Gastrointest. Res., Neurol. G., Ctr. of Excellence for Drug Discov., GlaxoSmithKline, New Frontiers Sci. Park, Third Ave., Harlow, Essex CM19 5AW, United Kingdom. nin_2_dass@gsk.com
SOURCE: British Journal of Pharmacology, (2003) 140/5 (948-954).
Refs: 24
ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 1 Following identification of the human **motilin receptor**, we isolated the rabbit orthologue by PCR amplification and found this to be 85% identical to the open reading frame of the human receptor. The protein encoded was 84% identical to the human polypeptide. 2 In HEK293T cells **transfected** with the rabbit receptor, motilin concentration-dependently increased intracellular calcium mobilisation (pEC(50) = 9.25). After transfection with G (ol)α, motilin similarly stimulated [(35)S]GTPγS binding (pEC(50) = 8.87). Using both systems, similar values were obtained with the human receptor, with rank-order potencies of motilin = [Nle(13)]-motilin > erythromycin; ghrelin was ineffective. 3 In circular muscle preparations of rabbit gastric antrum, [Nle(13)]- motilin 0.1-30 nM concentration-dependently increased the amplitude of electrically-evoked, neuronally-mediated contractions (pEC(50) = 8.3); higher concentrations increased the muscle tension (30-3000 nM). Both responses to [Nle(13)]-motilin faded rapidly during its continual presence. Rat or human ghrelin 0.01-10 μM were without activity. 4 Erythromycin 30-3000 nM and 10 μM, respectively, increased neuronal activity and muscle

tension in rabbit stomach. Unlike [Nle(13)]-motilin, the increase in neuronal activity did not fade during continual presence of submaximally-effective concentrations of erythromycin; some fade was observed at higher concentrations. 5 We conclude that the pharmacology of the rabbit **motilin receptor** is similar to the human orthologue and, when expressed as a recombinant, comparable to the native receptor. However, in terms of their ability to increase neuronal activity in rabbit stomach, [Nle(13)]-motilin and erythromycin are distinguished by different response kinetics, reflecting different rates of **ligand** degradation and/or interaction with the receptor.

L21 ANSWER 10 OF 10 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003445369 EMBASE
TITLE: High Constitutive Signaling of the Ghrelin Receptor - Identification of a Potent Inverse Agonist.
AUTHOR: Holst B.; Cygankiewicz A.; Jensen T.H.; Ankersen M.; Schwartz T.W.
CORPORATE SOURCE: Dr. B. Holst, Lab. for Molecular Pharmacology, Institute of Pharmacology, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen, Denmark. b.holst@molpharm.dk
SOURCE: Molecular Endocrinology, (2003) 17/11 (2201-2210). Refs: 47
ISSN: 0888-8809 CODEN: MOENEN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Ghrelin is a GH-releasing peptide that also has an important role as an orexigenic hormone-stimulating food intake. By measuring inositol phosphate turnover or by using a reporter assay for transcriptional activity controlled by cAMP-responsive elements, the ghrelin receptor showed strong, **ligand**-independent signaling in **transfected** COS-7 or human embryonic kidney 293 cells. Ghrelin and a number of the known nonpeptide GH secretagogues acted as agonists stimulating inositol phosphate turnover further. In contrast, the low potency ghrelin antagonist, [D-Arg(1),D-Phe(5),D-Trp (7,9),Leu(11)]-substance P was surprisingly found to be a high potency (EC(50) = 5.2 nM) full inverse agonist as it decreased the constitutive signaling of the ghrelin receptor down to that observed in untransfected cells. The homologous **motilin receptor** functioned as a negative control as it did not display any sign of constitutive activity; however, upon agonist stimulation the **motilin receptor** signaled as strongly as the unstimulated ghrelin receptor. It is concluded that the ghrelin receptor is highly constitutively active and that this activity could be of physiological importance in its role as a regulator of both GH secretion and appetite control. It is suggested that inverse agonists for the ghrelin receptor could be particularly interesting for the treatment of obesity.

=> d l19 ibib abs 1-391

L19 ANSWER 1 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2004-068645 [07] WPIDS
CROSS REFERENCE: 1996-464969 [46]; 1997-132787 [12]; 1998-101000 [09]
DOC. NO. CPI: C2004-028179
TITLE: Novel fluorescent peptide compound, useful for imaging cell receptor sites, cell sorting and flow cytometry.
DERWENT CLASS: B04 D16
INVENTOR(S): BONTER, K J; DESJARDINS, C; SLON-USAKIEWICZ, J
PATENT ASSIGNEE(S): (ADBI-N) ADVANCED BIOCONCEPT CO
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6677430	B1	20040113	(200407)*		14

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6677430	B1	CIP of	US 1995-504856	19950720
		CIP of	US 1996-682810	19960710
			US 2000-539593	20000331

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6677430	B1	CIP of	US 6054557

PRIORITY APPLN. INFO: US 2000-539593 20000331; US 1995-504856 19950720; US 1996-682810 19960710

AN 2004-068645 [07] WPIDS

CR 1996-464969 [46]; 1997-132787 [12]; 1998-101000 [09]

AB US 6677430 B UPAB: 20040128

NOVELTY - Fluorescent peptide compound (I) is new.

DETAILED DESCRIPTION - Fluorescent peptide compound of formula (I) is new.

R1 = light-emitting moiety;

R2 = motilin peptide, its fragment, derivative or analog (especially Phe-Val-Pro-IIe-Phe-Thr-Tyr-Gly-Glu-Leu-Gln-Arg-Met-Gln-Glu-Lys-Glu-Arg-Asn-Lys-Gly-Gln (S1));

(C-X) = C=O, C=S, CH (OH), C=C=O, C=NH, CH2, CH (OR), CH (NR), CH(R), CR3R4 or C(OR3) OR4; and

R, R3, R4 = alkyl moieties or substituted alkyl moieties.

In formula (I), R2 comprises the sequence of , where R2 is linked to (C-X) at an amino acid position selected such that (I) exhibits substantial biological activity in the presence of a receptor having affinity for motilin peptides.

INDEPENDENT CLAIMS are also included for the following:

(1) generating (I); and

(2) a kit for identifying target compounds for the treatment of motilin-related disease, comprising one of (I), and a receptacle containing a **motilin receptor** preparation.

USE - (I) is useful for labeling a receptor having an affinity for a motilin peptide by contacting the receptor with (I). (I) is useful for imaging cell receptor sites, which involves contacting candidate cell receptor sites with (I) and detecting the bound (I) as an indication of the cell receptor sites. (I) is useful for cell sorting, which involves contacting a population of candidate cell with (F), and isolating cells bound to (I). (I) is useful for flow cytometry, which involves contacting a population of cells with (I) and detecting cells bearing receptor on their surfaces by detecting cells bound to (I). (I) is useful for an assay of evaluating a known or candidate motilin agonist or antagonist molecule for receptor binding selectivity, which involves bringing together a molecule, (F), and a **motilin receptor** preparation containing **motilin receptors** capable of binding motilin, and determining or measuring the ability of the molecule to compete against (F) for binding to the **motilin receptor** preparation.

(I) is useful for an assay of determining the presence or amount of a **motilin receptor** binding molecule in a test sample, which involves bringing together the test sample and a **motilin receptor** preparation containing **motilin receptors** capable of binding motilin, measuring the ability of the

test sample to compete against (I) for binding to the **motilin receptor** preparation, and comparing the amount of **motilin receptor** binding molecule in the test sample to the amount of **motilin receptor** binding in a control sample.

(I) is useful for an assay of screening cell lines, cells desegregated from tissue, or cell membrane preparations, to identify those cells that carry **motilin receptors**, which involves contacting test cell lines, cells desegregated from tissue, or cell membrane preparations with (I), detecting an increase in fluorescent signal on the cell line, desegregated cell, or cell membrane preparation, compared to a negative control, where an increase in fluorescent signal indicates that a **motilin receptor** is present in the cell (claimed). (I) is useful for identifying, visualizing, quantifying, targeting and selecting receptors on cells and tissues both in vivo and in vitro.

(I) is useful for identifying, screening and characterizing potential motilin agonists and antagonists having therapeutic properties.

ADVANTAGE - (I) is safe, non-toxic and is conveniently used than other labeled peptides such as 125I radiolabeled peptides. (I) provides rapid, inexpensive and physiological processes for identifying, screening and characterizing potential motilin agonists and antagonists.

DESCRIPTION OF DRAWING(S) - The figure shows a schematic diagram of the chemical structure of fluorescently-labeled motilin peptide.

fluorescent peptide 10
light emitting moiety 12
peptide moiety 14

Dwg.1/2

L19 ANSWER 2 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:432844 BIOSIS
DOCUMENT NUMBER: PREV200300432844
TITLE: EM574, a motilide, has an orexigenic activity with affinity for growth-hormone secretagogue receptor.
AUTHOR(S): Asakawa, Akihiro [Reprint Author]; Inui, Akio [Reprint Author]; Ohinata, Kousaku; Fujimiya, Mineko; Meguid, Michael M.; Yoshikawa, Masaaki
CORPORATE SOURCE: Division of Diabetes, Digestive and Kidney Diseases, Department of Clinical Molecular Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan
SOURCE: Journal of Gastroenterology and Hepatology, (July 2003) Vol. 18, No. 7, pp. 881-882. print.
CODEN: JGHEEO. ISSN: 0815-9319.
DOCUMENT TYPE: Letter
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Sep 2003
Last Updated on STN: 17 Sep 2003

L19 ANSWER 3 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:485664 BIOSIS
DOCUMENT NUMBER: PREV200300485664
TITLE: Cyclopentene derivatives useful as antagonists of the **motilin receptor.**
AUTHOR(S): Chen, Robert H. [Inventor, Reprint Author]; Xiang, Min A. [Inventor]
CORPORATE SOURCE: ASSIGNEE: Ortho-McNeil Pharmaceutical, Inc.
PATENT INFORMATION: US 6624165 September 23, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sep 23 2003) Vol. 1274, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 2003
Last Updated on STN: 15 Oct 2003
AB The compounds of formula I are useful in treating gastrointestinal

disorders associated with antagonizing the **motilin receptor.** The compounds compete with erythromycin and motilin for the **motilin receptor.** In addition the compounds are antagonists of the contractile smooth muscle response to those ligands.

L19 ANSWER 4 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:354765 BIOSIS
DOCUMENT NUMBER: PREV200300354765
TITLE: Ethylamine derivatives.
AUTHOR(S): Matsuoka, Hiroharu [Inventor, Reprint Author]; Sato, Tsutomu [Inventor]
CORPORATE SOURCE: Shizuoka, Japan
ASSIGNEE: Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan
PATENT INFORMATION: US 6586630 July 01, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 1 2003) Vol. 1272, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jul 2003
Last Updated on STN: 30 Jul 2003
AB The object of the present invention is to provide ethylamine derivatives that function as a **motilin receptor** antagonist and that are useful as medicines. The invention provides compounds represented by the general formula (1): ##STR1## wherein R1 represents a phenyl group or the like, R2 represents a hydrogen atom and the like, R3 represents a hydrogen atom and the like, R4 represents a hydrogen atom and the like, R5 represents an alkyl group and the like, R7 represents a hydrogen atom and the like and R8 represents a heterocyclic ring and the like; or a hydrate or pharmaceutically acceptable salt thereof and a medicine which comprises the above compound or a hydrate or pharmaceutically acceptable salt thereof as an active ingredient.

L19 ANSWER 5 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:117737 BIOSIS
DOCUMENT NUMBER: PREV200300117737
TITLE: Substituted diamine derivatives useful as motilin antagonists.
AUTHOR(S): Johnson, Sigmond G. [Inventor, Reprint Author]; Rivero, Ralph A. [Inventor]
CORPORATE SOURCE: Flemington, NJ, USA
ASSIGNEE: Ortho McNeil Pharmaceutical, Inc.
PATENT INFORMATION: US 6511980 January 28, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan 28 2003) Vol. 1266, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 2003
Last Updated on STN: 26 Feb 2003
AB The present invention relates to novel substituted diamine derivatives for the formula ##STR1## wherein R1, R2, R3, R4, X1, X2, X3, X4, A, Y and n are as described in the specification, pharmaceutical compositions containing them and intermediates used in their manufacture. More particularly, the compounds of the invention are **motilin receptor** antagonists useful for the treatment of associated conditions and disorders such as gastrointestinal reflux disorders, eating disorders leading to obesity and irritable bowel syndrome.

L19 ANSWER 6 OF 391 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003514700 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 12907757
TITLE: High constitutive signaling of the ghrelin

receptor--identification of a potent inverse agonist.
AUTHOR: Holst Birgitte; Cygankiewicz Adam; Jensen Tine Halkjaer; Ankersen Michael; Schwartz Thue W
CORPORATE SOURCE: Laboratory for Molecular Pharmacology, Institute of Pharmacology, The Panum Institute, University of Copenhagen, DK-2200 Copenhagen, Denmark.. b.holst@molpharm.dk
SOURCE: Molecular endocrinology (Baltimore, Md.), (2003 Nov) 17 (11) 2201-10.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031101
Last Updated on STN: 20031219

AB Ghrelin is a GH-releasing peptide that also has an important role as an orexigenic hormone-stimulating food intake. By measuring inositol phosphate turnover or by using a reporter assay for transcriptional activity controlled by cAMP-responsive elements, the ghrelin receptor showed strong, ligand-independent signaling in transfected COS-7 or human embryonic kidney 293 cells. Ghrelin and a number of the known nonpeptide GH secretagogues acted as agonists stimulating inositol phosphate turnover further. In contrast, the low potency ghrelin antagonist, [D-Arg1,D-Phe5,D-Trp7,9,Leu11]-substance P was surprisingly found to be a high potency (EC50 = 5.2 nm) full inverse agonist as it decreased the constitutive signaling of the ghrelin receptor down to that observed in untransfected cells. The homologous **motilin receptor** functioned as a negative control as it did not display any sign of constitutive activity; however, upon agonist stimulation the **motilin receptor** signaled as strongly as the unstimulated ghrelin receptor. It is concluded that the ghrelin receptor is highly constitutively active and that this activity could be of physiological importance in its role as a regulator of both GH secretion and appetite control. It is suggested that inverse agonists for the ghrelin receptor could be particularly interesting for the treatment of obesity.

L19 ANSWER 7 OF 391 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003508897 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 14504130
TITLE: The rabbit **motilin receptor**: molecular characterisation and pharmacology.
AUTHOR: Dass N B; Hill J; Muir A; Testa T; Wise A; Sanger G J
CORPORATE SOURCE: Department of Gastrointestinal Research, Neurology and Gastroenterology Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK.. nin_2_dass@gsk.com
SOURCE: British journal of pharmacology, (2003 Nov) 140 (5) 948-54.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031031
Last Updated on STN: 20031219

AB Following identification of the human **motilin receptor**, we isolated the rabbit orthologue by PCR amplification and found this to be 85% identical to the open reading frame of the human receptor. The protein encoded was 84% identical to the human polypeptide. In HEK293T cells transfected with the rabbit receptor, motilin concentration-dependently increased intracellular calcium mobilisation (pEC50=9.25). After transfection with Go1alpha, motilin similarly stimulated [35S]GTPgammaS binding (pEC50=8.87). Using both systems, similar values were obtained with the human receptor, with rank-order potencies of

motilin=[Nle13]-motilin>erythromycin; ghrelin was ineffective. In circular muscle preparations of rabbit gastric antrum, [Nle13]-motilin 0.1-30 nM concentration-dependently increased the amplitude of electrically-evoked, neuronally-mediated contractions (pEC50=8.3); higher concentrations increased the muscle tension (30-3000 nM). Both responses to [Nle13]-motilin faded rapidly during its continual presence. Rat or human ghrelin 0.01-10 microM were without activity. Erythromycin 30-3000 nM and 10 microM, respectively, increased neuronal activity and muscle tension in rabbit stomach. Unlike [Nle13]-motilin, the increase in neuronal activity did not fade during continual presence of submaximally-effective concentrations of erythromycin; some fade was observed at higher concentrations. We conclude that the pharmacology of the rabbit **motilin receptor** is similar to the human orthologue and, when expressed as a recombinant, comparable to the native receptor. However, in terms of their ability to increase neuronal activity in rabbit stomach, [Nle13]-motilin and erythromycin are distinguished by different response kinetics, reflecting different rates of ligand degradation and/or interaction with the receptor.

L19 ANSWER 8 OF 391 EMBASE
on STN

ACCESSION NUMBER: 2003185701 EMBASE
TITLE: New developments in the treatment of functional dyspepsia.
AUTHOR: Stanghellini V.; De Ponti F.; De Giorgio R.; Barbara G.; Tosetti C.; Corinaldesi R.
CORPORATE SOURCE: Dr. V. Stanghellini, Dept. of Int. Med./Gastroenterology, University of Bologna, Policlinico S. Orsola-Malpighi, Via Massarenti 9, Bologna I-40138, Italy. vstang@med.unibo.it
SOURCE: Drugs, (2003) 63/9 (869-892).
Refs: 180
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Functional dyspepsia is a clinical syndrome defined by chronic or recurrent pain or discomfort in the upper abdomen of unknown origin. Although generally accepted, investigators differently interpret this definition and clinical trials are often biased by inhomogeneous inclusion criteria. The poorly defined multifactorial pathogenesis of dyspeptic symptoms has hampered efforts to develop effective treatments. A general agreement exists on the irrelevant role played by Helicobacter pylori in the pathophysiology of functional dyspepsia. Gastric acid secretion is within normal limits in patients with functional dyspepsia but acid related symptoms may arise in a subgroup of them. Proton pump inhibitors appear to be effective in this subset of patients with dyspepsia. Non-painful dyspeptic symptoms are suggestive of underlying gastrointestinal motor disorders and such abnormalities can be demonstrated in a substantial proportion of patients. Postprandial fullness and vomiting have been associated with delayed gastric emptying of solids, and early satiety and weight loss to postcibal impaired accommodation of the gastric fundus. Prokinetics have been shown to exert beneficial effects, at least in some patients with dyspepsia. In contrast, drugs enhancing gastric fundus relaxation have been reported to improve symptoms, although conflicting results have also been published. An overdistended antrum may also generate symptoms, but its potential pathogenetic role and the effects of drugs on this abnormality have never been investigated formally. Visceral hypersensitivity plays a role in some dyspeptic patients and this abnormality is also a potential target for treatment. Both chemo- and mechanoreceptors can trigger hyperalgesic responses. Psychosocial abnormalities have been consistently found in

functional digestive syndromes, including dyspepsia. Although useful in patients with irritable bowel syndromes (IBS), antidepressants have been only marginally explored in functional dyspepsia. Among the new potentially useful agents for the treatment of functional dyspepsia, serotonin 5-HT(4) receptor agonists have been shown to exert a prokinetic effect. Unlike motilides, 5-HT(4) receptor agonists do not appear to increase the gastric fundus tone and this may contribute to improve symptoms. 5-HT(3) receptor antagonists have been investigated mainly in the IBS and the few studies performed in functional dyspepsia have provided conflicting results. Also, κ-opioid receptor agonists might be useful for functional digestive syndromes because of their antinociceptive effects, but available results in functional dyspepsia are scanty and inconclusive. Other receptors that represent potential clinical targets for antagonists include purinoceptors (i. e., P2X2/3 receptors), NMDA receptors (NR2B subtype), protease-activated receptor-2, the vanilloid receptor-1, tachykinin receptors (NK(1)/NK(2)) and cholecystokinin (CCK)(1) receptors.

L19 ANSWER 9 OF 391 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003418832 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12958653
TITLE: Involvement of dopamine D3 and neuropeptide Y Y5 receptors in diabetic gastroparetic rats without response to erythromycin.
AUTHOR: Qin Xin-Yu; Wang Zhi-Gang; Fei Jian; Liu Feng-Lin; Cui Da-Fu; Chen Shao-Liang
CORPORATE SOURCE: Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China.. xyqin@zshospital.com
SOURCE: Sheng wu hua xue yu sheng wu wu li xue bao Acta biochimica et biophysica Sinica, (2003 Sep) 35 (9) 811-5. Journal code: 20730160R. ISSN: 0582-9879.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030906
Last Updated on STN: 20040131
Entered Medline: 20040130

AB Erythromycin may accelerate gastric emptying in animals and human probably as an motilin agonist, but its prokinetic effects show obvious individual disparity. This study was to find the mechanism of this phenomenon. Microarray analysis was used to screen genes that might be involved in the response of diabetic gastroparesis rats to erythromycin. It was found that erythromycin accelerated gastric emptying of diabetic rats with great individual disparity. Through microarray analysis we screened differential expression genes that might be involved in the effect of erythromycin. Among 10 genes screened out, dopamine D3 receptor (DRD3) and neuropeptide Y Y5 receptor (NPYY5) genes were submitted to RT-PCR quantification and showed consistent results with microarray. It can be concluded that erythromycin promote gastric emptying of gastroparetic rats; DRD3 and NPYY5 may be involved in prokinetic action of erythromycin; and targets other than **motilin receptor** of erythromycin might exist as prokinetics.

L19 ANSWER 10 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2003329438 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12858612
TITLE: Pharmacotherapy for intestinal motor and sensory disorders.
AUTHOR: Hasler William L
CORPORATE SOURCE: Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical Center, 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109, USA.. whasler@umich.edu
CONTRACT NUMBER: 1 K24 DK02726-01 (NIDDK)

SOURCE: Gastroenterology clinics of North America, (2003 Jun) 32 (2) 707-32, viii-ix. Ref: 124
Journal code: 8706257. ISSN: 0889-8553.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030716
Last Updated on STN: 20031218
Entered Medline: 20031126

AB Motor disorders of the gastrointestinal tract are characterized by definable impairments of gut contractile function. Other conditions exhibit specific disturbances of visceral afferent and efferent activity, which may underlie selected symptom complexes. Medications in several classes have been developed to treat these disorders of gastrointestinal function. Prokinetic agents are effective therapies for ailments with reduced motor function, whereas antispasmodic drugs reduce symptoms in conditions with exaggerated pressure wave activity. Recently, medications designed to blunt transmission in visceral sensory pathways have been proposed for use in the functional bowel disorders. Finally, some patients may benefit from initiation of nonspecific therapies, which have no appreciable effect on gut motor or sensory function.

L19 ANSWER 11 OF 391 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003185687 MEDLINE
DOCUMENT NUMBER: 22590611 PubMed ID: 12606621
TITLE: Interaction of the growth hormone-releasing peptides ghrelin and growth hormone-releasing peptide-6 with the **motilin receptor** in the rabbit gastric antrum.
AUTHOR: Depoortere Inge; Thijs Theo; Thielemans Leen; Robberecht Patrick; Peeters Theo L
CORPORATE SOURCE: Department of Pathophysiology, Centre for Gastroenterological Research, University of Leuven, Leuven, Belgium.. inge.depoortere@med.kuleuven.ac.be
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2003 May) 305 (2) 660-7.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030422
Last Updated on STN: 20030531
Entered Medline: 20030530

AB The structural relationship between the motilin and the growth hormone secretagogue receptor (GHS-R), and between their respective ligands, motilin and ghrelin, prompted us to investigate whether ghrelin and the GHS-R agonist growth hormone-releasing peptide-6 (GHRP-6), could interact with the **motilin receptor.** The interaction was evaluated in the rabbit gastric antrum with binding studies on membrane preparations and with contraction studies on muscle strips in the presence of selective antagonists under conditions of electrical field stimulation (EFS) or not. Binding studies indicated that the affinity (pK(d)) for the **motilin receptor** was in the order of ghrelin (4.23 +/- 0.07) < GHRP-6 (5.54 +/- 0.08) < motilin (9.13 +/- 0.03). The interaction of ghrelin with the **motilin receptor** requires the octanoyl group. Motilin induced smooth muscle contractile responses but ghrelin and GHRP-6 were ineffective. EFS elicited on- and off-responses that were increased by motilin already at 10(-9) M, but not by 10(-5) M ghrelin. In contrast, GHRP-6 also enhanced the on- and off-responses.

The motilin antagonist Phe-cyclo[Lys-Tyr(3-tBu)-betaAla-] trifluoroacetate (GM-109) blocked the effect of GHRP-6 on the off-responses but not on the on-responses. Under nonadrenergic noncholinergic conditions, the effects of motilin and GHRP-6 on the on-responses were abolished; those on the off-responses were preserved. All responses were blocked by neurokinin (NK)(1) and NK(2) antagonists. In conclusion, ghrelin is unable to induce contractions via the **motilin receptor.** However, GHRP-6 enhances neural contractile responses, partially via interaction with the **motilin receptor** on noncholinergic nerves with tachykinins as mediator, and partially via another receptor that may be a GHS-R subtype on cholinergic nerves that corelease tachykinins.

L19 ANSWER 12 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:544924 SCISEARCH
THE GENUINE ARTICLE: 689PF
TITLE: Erythromycin induces pyloric relaxation accompanied by a contraction of the gastric body after pylorus-preserving gastrectomy
AUTHOR: Nakabayashi T; Mochiki E (Reprint); Kamiyama Y; Haga N; Asao T; Kuwano H
CORPORATE SOURCE: Gunma Univ, Fac Med, Dept Surg 1, 3-39-22 Showa Machi, Maebashi, Gumma 3718511, Japan (Reprint); Gunma Univ, Fac Med, Dept Surg 1, Maebashi, Gumma 3718511, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: SURGERY, (JUN 2003) Vol. 133, No. 6, pp. 647-655. Publisher: MOSBY, INC, 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA. ISSN: 0039-6060.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 32
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Pylorus-preserving gastrectomy (PPG) is a function-preserving surgery; however, long-term retention of food in the residual stomach is a frequent complication during the early postoperative period. We reported that gastric stasis after PPG was attributable to the delayed recovery of gastric phase III, in which pyloric relaxation accompanied a contraction of the gastric body. The objective of the present study is to determine whether erythromycin can induce phase III with pyloric relaxation after PPG.

Methods. We studied gastrointestinal motility in dogs after PPG by using strain gauge force transducer. After randomized administration of either erythromycin or saline, interdigestive gastropyloroduodenal motility was recorded.

Results. Erythromycin induced phase X with pyloric relaxation in the early postoperative period. Pyloric relaxation accompanied a contraction of the gastric body. Compared with the saline group (body: 87.2 +/- 16.7 mmHg X min, antrum: 69.7 +/- 13.7 mmHg X min, pylorus: 91.7 +/- 22.1 mmHg X min), the erythromycin group showed significantly increased gastropyloric motility indexes (body: 5062 +/- 33.5 mmHg X min, antrum: 430.9 +/- 53.7 mmHg X min, pylorus: 589.5 +/- 59.5 mmHg X min).

Conclusion. Erythromycin can induce phase III, in which pyloric relaxation, accompanied a contraction of the gastric body in the early postoperative Period after PPG. Erythromycin might be used as a prokinetic agent for the treatment of early gastric stasis after PPG.

L19 ANSWER 13 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:712702 CAPLUS
DOCUMENT NUMBER: 140:53538
TITLE: Identification of ligand-binding domains of **motilin receptor**
AUTHOR(S): Matsuura, Bunzo
CORPORATE SOURCE: The Third Department of Internal Medicine, Ehime University School of Medicine, Ehime-ken, 791-0295, Japan

SOURCE: Shokakika (2003), 36(5), 413-416
CODEN: SHOKCB; ISSN: 0289-8756
PUBLISHER: Kagaku Hyoronsha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, on secondary structure and methods for anal. of mechanism of **motilin receptor**-ligand binding.

L19 ANSWER 14 OF 391 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003420898 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 12960650
TITLE: Erythromycin fails to improve feeding outcome in feeding-intolerant preterm infants.
AUTHOR: ElHennawy Adel A; Sparks John W; Armentrout Debra; Huseby Valerie; Berseth Carol Lynn
CORPORATE SOURCE: Department of Pediatrics, University of Texas Health Science Center at Houston, Houston, Texas, USA.
SOURCE: Journal of pediatric gastroenterology and nutrition, (2003 Sep) 37 (3) 281-6.
Journal code: 8211545. ISSN: 0277-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030909
Last Updated on STN: 20031218
AB OBJECTIVE: Approximately half of extremely low birth weight infants have feeding intolerance, which delays their achievement of full enteral feedings. Erythromycin, a **motilin receptor** agonist, triggers migrating motor complexes and accelerates gastric emptying in adults with feeding intolerance. Few studies have assessed the efficacy of this drug in preterm infants with established feeding intolerance. This study was designed to assess the efficacy of erythromycin in feeding-intolerant infants, as measured by gastric emptying, maturation of gastrointestinal motor patterns, and time to achieve full enteral feedings. METHODS: Subjects were 27 preterm infants who were admitted to the neonatal intensive care unit and who did not achieve full enteral feeding volumes (150 mL/kg/day) within 8 days of the initiation of feedings. In a controlled, randomized, double-blinded clinical trial, infants received intragastric erythromycin or placebo for 8 days without crossover. At study entry, the authors recorded motor activity in the antrum and the duodenum during fasting, in response to intragastric erythromycin (1.5 mg/kg) or placebo, and in response to feeding. Gastric emptying at 20 minutes and transit time from duodenum to anus were determined. Each infant then received erythromycin or placebo for 8 days, and feeding characteristics were prospectively tracked. RESULTS: Gastric emptying and characteristics of antroduodenal motor contractions were similar in the two groups, as were the transit times from duodenum to anus. Feeding outcomes were comparable in the two groups. CONCLUSION: Intragastric erythromycin does not improve feeding tolerance in preterm infants with established feeding intolerance because it fails to improve gastrointestinal function in the short or long term.

L19 ANSWER 15 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:307972 BIOSIS
DOCUMENT NUMBER: PREV200300307972
TITLE: **Motilin receptors** in the human cardiovascular system.
AUTHOR(S): Kuc, R. E. [Reprint Author]; Davies, I. C. [Reprint Author]; Davenport, A. P. [Reprint Author]
CORPORATE SOURCE: Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Box 110, Cambridge, CB2 2QQ, UK
SOURCE: British Journal of Pharmacology, (April 2003) Vol. 138, No. Proceedings Supplement, pp. 165P. print.
Meeting Info.: Proceedings of the British Pharmacological

Society Meeting. Brighton, UK. January 08-10, 2003. British Pharmacological Society.
ISSN: 0007-1188 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003

L19 ANSWER 16 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:776998 SCISEARCH
THE GENUINE ARTICLE: 675CR
TITLE: Motilin and erythromycin-A share a common winding site in the third transmembrane segment of the **motilin receptor**
AUTHOR: Xu L (Reprint); Depoortere I; Vertongen P; Thielemans L; Perret J; Waelbroeck M; Robberecht P; Peeters T
SOURCE: GASTROENTEROLOGY, (APR 2003) Vol. 124, No. 4, Supp. [S], pp. A136-A136.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 17 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:620005 SCISEARCH
THE GENUINE ARTICLE: 667GT
TITLE: **Motilin receptors** in the human cardiovascular system
AUTHOR: Kuc R E (Reprint); Davies I C; Davenport A P
CORPORATE SOURCE: Univ Cambridge, Addenbrookes Hosp, Clin Pharmacol Unit, Cambridge CB2 2QQ, England
COUNTRY OF AUTHOR: England
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (APR 2003) Vol. 138, Supp. [S], pp. U83-U83. MA 165P.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.
ISSN: 0007-1188.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 3

L19 ANSWER 18 OF 391 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2003326933 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 12856827
TITLE: Effect of erythromycin on contractile response of uterine smooth muscle strips in non-pregnant rats.
AUTHOR: Liu Heng; Zhu Tianmin; Ma Yongming; Qu Songyi
CORPORATE SOURCE: Cell Biology Institute, Life Science School, Lanzhou University, Lanzhou 730000, Gansu, PR China..
hliu_kong@yahoo.com
SOURCE: Polish journal of pharmacology, (2003 Jan-Feb) 55 (1) 57-62.
Journal code: 9313882. ISSN: 1230-6002.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030715
Last Updated on STN: 20031218
AB OBJECTIVE: Erythromycin stimulates stomach smooth muscle contraction via action on **motilin receptors**, but the effects of erythromycin on non-pregnant uterine smooth muscle are unknown. The

purpose of this study was to assess the effect of erythromycin on non-pregnant uterine smooth muscle and to examine the possible mechanism of its action. STUDY DESIGN: Uterine smooth muscle strips from rats were suspended in organ baths containing Krebs solution, and then isometric tension was measured. The response to erythromycin and the effect of hexamethonium, indomethacin, phentolamine, diphenhydramine, atropine, metoclopramide and verapamil on erythromycin-induced contraction were also assessed. RESULTS: The present study showed for the first time that erythromycin dose-dependently increased contractile frequency, and at a dose of 1.55 x 10(-3) mol/l it also increased contractile tension in non-pregnant uterine smooth muscle strips in rats. These actions were not affected by pretreatment with hexamethonium, indomethacin, phentolamine, atropine and metoclopramide, but histamine H1 receptor blocker diphenhydramine and calcium channel blocker verapamil inhibited both responses induced by erythromycin. CONCLUSION: Our results suggest that erythromycin could increase contractile frequency and tension of non-pregnant uterine smooth muscle via histamine H1 receptor and calcium channel.

L19 ANSWER 19 OF 391 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2003395518 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12932837
TITLE: Excitatory effects of motilin in the hippocampus on gastric motility in rats.
AUTHOR: Guan Yanfang; Tang Ming; Jiang Zhengyao; Peeters Theo L
CORPORATE SOURCE: Department of Physiology, Medical College of Qingdao University, Qingdao, 266021, PR China.. guan_yanfang@yanhoo.com
SOURCE: Brain research, (2003 Sep 12) 984 (1-2) 33-41. Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20030823
Last Updated on STN: 20031218
Entered Medline: 20031210
AB Intestinal motilin is known to stimulate gastrointestinal motility. Recently, it was shown that the motilin gene and the **motilin receptor** are expressed in various regions of the brain. We studied whether motilin can activate pathways in the rat hippocampus to stimulate gastric motility. Gastric motility was monitored in conscious rats, whereas extracellular electrical activity recordings of the hippocampus were performed on anaesthetized rats to measure the influence of microinjection of motilin and CCK-8 into the hippocampus and into the cerebral ventricles. We found that neurons in the CA3 region of the hippocampus are sensitive to gastric distension, and that injection of motilin into the hippocampus increased the amplitude of gastric contractions by 35.3+/-6.8%, while CCK-8 injection inhibited motility by -27.3+/-6.8%. The hippocampal motilin-induced stimulation of gastric motility (30.6+/-5.5%) was completely abolished by subdiaphragmal vagotomy (-2.8+/-4.4%) but unaffected by the intravenously applied receptor blockers atropine, phentolamine and propranolol. In vivo extracellular recordings of gastric distension-responsive CA3 neurons revealed that intracerebroventricular administration of motilin increased firing while CCK-8 inhibited firing. These opposite effects of motilin and CCK-8 fit with the nature of the actions of these gut-brain peptides on gastric motility. Our findings suggest that the stimulation of gastric motility by motilin administered in the hippocampus reflects the existence of a functional interaction between the hippocampus and a vago-vagus reflex running via a noncholinergic and nonadrenergic efferent pathway.

L19 ANSWER 20 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2003016672 MEDLINE

DOCUMENT NUMBER: 22410916 PubMed ID: 12523456
TITLE: Erythromycin accelerates gastric emptying in a dose-response manner in healthy subjects.
AUTHOR: Boivin Michel A; Carey Michael C; Levy Howard
CORPORATE SOURCE: Division of Pulmonary and Critical Care, Department of Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, USA.. mboivin@salud.unm.edu
CONTRACT NUMBER: 5M01 RR00997 (NCRR)
SOURCE: PHARMACOTHERAPY, (2003 Jan) 23 (1) 5-8.
Journal code: 8111305. ISSN: 0277-0008.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030114
Last Updated on STN: 20030417
Entered Medline: 20030416

AB STUDY OBJECTIVES: To evaluate whether a dose-response curve exists for erythromycin, determine the lowest effective dose of erythromycin needed to improve gastric motility, and compare erythromycin's effectiveness with that of metoclopramide in improving gastric emptying. DESIGN: Randomized, crossover, multiintervention trial. SETTING: Inpatient clinical research center. SUBJECTS: Ten healthy volunteers (four men, six women) from the general population. INTERVENTION: On each study day, the subjects were infused with erythromycin 0.75 mg/kg, 1.5 mg/kg, or 3.0 mg/kg; metoclopramide 10 mg; or placebo, in random order. Subjects then drank Ensure 200 ml mixed with acetaminophen 1.5 g. Gastric emptying was estimated by comparing the area under the curve after 60 minutes for acetaminophen absorption using four timed blood draws. MEASUREMENTS AND MAIN RESULTS: Erythromycin increased gastric emptying in a dose-response manner. Erythromycin 3.0 mg/kg and metoclopramide 10 mg were associated with statistically significant increases in liquid gastric emptying compared with placebo. During infusion, nausea and stomach cramping were associated with the 3.0-mg/kg dose of erythromycin; drowsiness was associated with metoclopramide. CONCLUSION: In patients requiring intravenous erythromycin for gastric motility, the 3.0-mg/kg dose seems the most effective, with a reasonable side effect profile.

L19 ANSWER 21 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:776331 SCISEARCH
THE GENUINE ARTICLE: 675CR
TITLE: Differences in the ability of motilides to induce **motilin receptor** internalization underly their desensitizing capacity
AUTHOR: Thielemans L (Reprint); Perret J; Depoortere I; Robberecht P; Peeters T L
SOURCE: GASTROENTEROLOGY, (APR 2003) Vol. 124, No. 4, Supp. [S], pp. A1-A1.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 22 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:583803 BIOSIS
DOCUMENT NUMBER: PREV200300573482
TITLE: THE EFFECT OF RWJ 68023, A NOVEL MOTILIN ANTAGONIST, ON RABBIT SMALL INTESTINAL MOTILITY.
AUTHOR(S): Otterson, Mary F. [Reprint Author]; Leming, Shawn; Gunnet, Joseph; Hageman, William

CORPORATE SOURCE: Milwaukee, WI, USA
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. S1150. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003

AB RWJ68023 is a potent, non-peptide antagonist of the **motilin receptor.** RWJ68023 antagonized both motilin & erythromycin induced contractions in rabbit duodenum smooth muscle strips in vitro. Because this compound does not antagonize acetylcholine-induced contractions of rabbit longitudinal duodenal smooth muscle or KCl-induced contractions of rabbit aorta in vitro, it is felt to be specific for the **motilin receptor.** The in vivo effects were unknown. Methods: We investigated RWJ68023 in 5 rabbits instrumented with 5 strain gauges located between 15 & 95 cm distal to the pylorus. The area under the curve of contractions was used & expressed as the mean + SEM. Two additional rabbits were instrumented with gastric & small intestinal gauges. Prior to recording, food was withdrawn for 2 h. Motilin was administered IV as a bolus. RWJ68023 or saline was administered as an infusion over 2 min 5 min following motilin. Results were analyzed using ANOVA. Results: Spontaneous MMCs occur in rabbit small intestine & propagate at a velocity of 3.2 cm/min. Gastric cyclic motor activity does not occur in conjunction with small intestinal MMCs. RWJ68023 produced no effect on spontaneous gastric or small intestinal motor activity. A dose response curve was performed to identify the motilin dose required to produce a contractile response. 700 ng/kg motilin was the lowest dose that produced contractions throughout the first 95 cm of small intestine. At doses of 200-600 ng/kg, contractions were less regular in the distal gauges. Contractions occurred nearly simultaneously & were delayed 19 sec between the first & the last strain gauge following 700 ng/kg of motilin. 15 mg/kg RWJ68023 5 min prior to 700 ng/kg of motilin partially blocked the effect of motilin at 15 cm distal to the pylorus ($p<0.05$, see table). 5 & 10mg/kg RWJ68023 did not significantly decrease activity at 15 cm. In the more distal small intestine, response to RWJ68023 was variable. Conclustions: The present in vivo data confirms that this compound, RWJ68023, is a **motilin receptor** antagonist. RWJ68023 may be used as a pharmacological tool to further investigate the regulation & function of motilin in gastrointestinal contractile activity. Variability of blockade by RWJ68023 beyond the duodenum may reflect receptor density..

L19 ANSWER 23 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:26199 BIOSIS
DOCUMENT NUMBER: PREV200400024585
TITLE: DIRECT IDENTIFICATION OF A DISTINCT SITE OF APPROXIMATION BETWEEN RESIDUE FIVE OF MOTILIN AND ITS RECEPTOR USING INTRINSIC PHOTOAFFINITY LABELING. .
AUTHOR(S): Matsuura, Bunzo [Reprint Author]; Dong, Maoqing; Matsui, Hidetaka; Onji, Morikazu; Coulie, Bernard; Hadac, Elizabeth; Pinon, Delia I.; Miller, Laurence J.
CORPORATE SOURCE: AZ, Japan
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. T1021. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 2003
Last Updated on STN: 31 Dec 2003

AB The **motilin receptor** belongs to a recently recognized group of class I G protein-coupled receptors that also includes the growth hormone secretagogue receptors. These represent clinically useful targets for pharmacotherapy. Their potentially unique structure and the molecular basis of their binding are not yet clear. We recently reported the first affinity labeling of a domain within this receptor using a photolabile analogue of motilin with site of covalent attachment at the peptide amino-terminus (J. Biol. Chemical 276:35518, 2001). That probe labeled a cyanogen bromide fragment of the receptor extending from the predicted first to the second extracellular loop domain. To extend our understanding of the molecular basis of motilin binding, we have developed an additional radioiodinatable motilin analogue probe having site of covalent attachment in position five. This was a full agonist that bound to the **motilin receptor** specifically and with high affinity, and that efficiently established a single covalent bond. Sequential chemical and enzymatic cleavage of the labeled wild type and mutant pseudo-wild type **motilin receptor** constructs established that the domain of labeling was within the third extracellular loop. This was further localized to a single residue using radiochemical Edman degradation sequencing. These data provide the first specific constraint that can be utilized in the docking of this peptide ligand to its receptor. We hope that a series of such constraints can be determined to provide adequate structural information to begin to elucidate the conformation of this agonist-bound receptor, and to ultimately be useful in the rational design of drugs acting at this important target..

L19 ANSWER 24 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:580756 BIOSIS
DOCUMENT NUMBER: PREV200300571371
TITLE: MOTILIN AND ERYTHROMYCIN-A SHARE A COMMON BINDING SITE IN THE THIRD TRANSMEMBRANE SEGMENT OF THE **MOTILIN RECEPTOR.** .
AUTHOR(S): Xu, Luo [Reprint Author]; Depoortere, Inge; Vertongen, Pascale; Thielemans, Leen; Perret, Jason; Waelbroeck, Magali; Robberecht, Patrick; Peeters, Theo
CORPORATE SOURCE: Leuven, Belgium
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. S1010. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003

AB The **motilin receptor** (MTL-R) represents a clinically useful pharmacological target, activated by the gastroprokinetic agent erythromycin-A (EM-A). We aimed at comparing the molecular basis for interaction of the MTL-R with motilin and with the non-peptide motilin agonist EM-A, by site-directed mutagenesis. Methods. The negatively charged Glu119 in the third transmembrane (TM-3) region of the MTL-R was selected as potential candidate for interaction with the positive charge on the amine of Phe1 in motilin and the desosamine of EM-A, and was mutated to Gln (E119Q) or Asp (E119D). Each mutant was stably transfected in CHO-cells containing the Ca2+ indicator apo-aequorin. Receptor activation in response to motilin, motilin fragments, EM-A and EM-A

derivatives was assessed by Ca2+-induced luminescence. Results. In the E119Q mutant the Ca2+ response to motilin and EM-A was abolished while in the E119D mutant it was reduced to respectively 30+-2% and 13+-1%. The pEC50 values for motilin and EM-A were shifted from respectively 9.61+-0.05 and 6.99+-0.21 in the wild type (WT) receptor to 7.58+-0.15 and 4.77+-0.23 in the E119D mutant. The reduced potency of motilin fragment (1-14) (WT receptor: 8.14+-0.09; E119D mutant: 5.85+-0.41) could be reversed by methylation of its N-terminal amine group both in the WT receptor (one methyl: 9.37+-0.10; two methyls: 9.18+-0.15) and in the E119D mutant (one methyl: 6.38+-0.08; two methyls: 7.91+-0.05). However, with a third methyl group potency was again lower in the WT receptor (8.68+-0.36) and absent in the mutant. A similar effect was obtained by acetylation of the amino terminus: 7.42+-0.22 (WT); inactive (E119D mutant). The potency of EM-A and EM-A enolether was reduced respectively from 6.99+-0.21 and 8.07+-0.02 in the WT receptor to 4.77+-0.23 and 5.91+-0.78 in the E119D mutant. Acetylation of the N-dimethylamino group in EM-A enolether also resulted in an inactive compound in the E119D mutant. Conclusion. In contrast to previous studies (Matsuura, JBC 277: 9834-39, 2002) our results indicate that motilin and EM-A share a common binding site in TM-3 of the MTL-R involving an ionic interaction between the positive charge on the basic amine of the agonist and the negative charge on Glu119. This interaction is lost when either the negative charge is removed, as in the E119Q mutant, or the positive charge, as in the acetylated agonists..

L19 ANSWER 25 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:583438 BIOSIS
DOCUMENT NUMBER: PREV200300573246
TITLE: THE C-TERMINAL DOMAIN OF MOTILIN IS REQUIRED FOR COMPLETE HOMOLOGOUS DESENSITIZATION AND ENDOCYTOSIS.
AUTHOR(S): Thielemans, Leen [Reprint Author]; Perret, Jason; Depoortere, Inge; Robberecht, Patrick; Peeters, Theo L.
CORPORATE SOURCE: Leuven, Belgium
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 856. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003

AB Background. The bioactive part of motilin (22 AA) resides in the N-terminal end. Aim. To investigate whether the same portion of motilin is sufficient for desensitizing the **motilin receptor** (MTLR). Methods. Agonist induced Ca2+ luminescence was studied in CHO-K1 cells expressing the **motilin receptor** and the Ca2+ indicator apoaequorin. Desensitization was studied by preincubation of the cells with motilin or motilin fragments prior to a second stimulation with motilin. Results were expressed as a % of control response (no prestimulation). Internalization was visualized in CHO-K1 cells containing a C-terminal enhanced green fluorescent protein (EGFP)-tagged MTLR. Scion Image Software was used to quantify changes in fluorescence on the membrane and in the cytosol. Radio-iodinated motilin was used to determine the % of non-internalized receptors on the cells by measuring residual binding after prestimulation with agonists. Results. Motilin fragment (1-14) (pEC50: 8.50) was almost as potent as the full-length motilin (1-22) (pEC50: 9.00) to induce a Ca2+ luminescent response. Preincubation with motilin reduced dose-dependently the maximal Ca2+ response to a second stimulation with motilin to 99+-7% (10-9 M), 72+-8% (10-8 M), 47+-5% (10-7 M), 27+-2% (10-6 M) and 9+-1%. (10-5 M). In contrast, fragment (1-14) reduced the Ca2+ response to motilin only to

69+-13% at 10-4M. Fragment (1-19) only desensitized at a minimum of 10-5M (61+-5%), and 10-4 M was required for fragment (1-16) (4+-2%). The less potent fragments (1-5), (1-7), (1-9) did not significantly desensitize the MTLR at 10-4M, neither did the C-terminal fragments (12-22), (10-22), (3-22), (15-22). Likewise the central fragments (7-19) and (5-17) were without effect at 10-4 M or lower. Studies with the EGFP-tagged **motilin receptor** showed that the fluorescence at the membrane was decreased by 19+-2% after preincubation with motilin but not with fragment (1-14). For motilin this was accompanied by an increase of 22+-2 % in cytosolic fluorescence while for motilin (1-14) this was only 11+-3 % (P< 0.0001). Similarly, receptor binding studies confirmed that residual binding after preincubation with motilin was only 31+-3 % compared to 54+-3% and 75+-3% with fragments (1-19) and (1-14) resp. Conclusion. None of the inactive fragments desensitizes the MTLR. However, the ability to activate is not sufficient as the minimal portion required for activation (1-14) has to be extended C-terminally to induce more substantial desensitization and endocytosis..

L19 ANSWER 26 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:583422 BIOSIS
DOCUMENT NUMBER: PREV200300573230
TITLE: DIFFERENCES IN THE ABILITY OF MOTILIDES TO INDUCE **MOTILIN RECEPTOR** INTERNALIZATION UNDERLY THEIR DESENSITIZING CAPACITY .
AUTHOR(S): Thielemans, Leen [Reprint Author]; Perret, Jason; Depoortere, Inge; Robberecht, Patrick; Peeters, Theo L.
CORPORATE SOURCE: Leuven, Belgium
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 23. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 2003
Last Updated on STN: 10 Dec 2003

AB Background. There are marked differences in the ability to desensitize the motiline receptor (MTLR) between the motilides ABT-229 and erythromycin-A (EM-A), which cannot be explained by differences in potency (Gastroenterol., 2002, 122 (4) W1030). Aim. To explore whether this translates into differences in MTLR internalization. Methods. A CHO-K1 cell line containing the Ca2+ indicator apoaequorin was stably transfected with a plasmid containing MTLR C-terminally tagged with EFGP (Enhanced Green Fluorescent Protein). Desensitization was studied by preincubation of the cells with 10-5 M of motilin, EM-A or ABT-229 prior to stimulation with motilin. The maximal response to the second stimulation was expressed as a percentage of control (no prestimulation). For visualization of endocytosis, images of stimulated cells were analyzed by the Scion Image Software. Internalization was also quantified by determining residual binding of radio-iodinated motilin after prestimulation with agonists. Results. The maximal response to motilin was reduced to 19 +- 2 and 3 +- 1 % after prestimulation with motilin or ABT-229, but was barely affected after EM-A (99 +- 8 %). Pictures of cells before and after stimulation for 1h at 37degreeC show that all agonists (10-5 M) induced significant (at least p<0.005) changes in the distribution of the MTLR. Membrane fluorescence significantly decreased by 16 +- 2, 25 +- 2 and 8 +- 2 % for motilin, ABT-229 and *EM-A resp (p<0.0001; *p=0.04 vs control), while cytosol fluorescence increased by 24 +- 2, 25 +- 2 and 19 +- 2% (p<0.0001 vs control). Receptor binding studies confirmed that stimulation for 1h at 37degreeC with EM-A did not induce MTLR internalization, as residual binding remained at 96 +- 4% compared to 31 +- 3% and 21 +- 1% after stimulation with motilin and

ABT-229. Conclusion. The extent of receptor internalization for ABT-229, motilin and EM-A corresponds to their ability to desensitize the **motilin receptor.** The strong desensitizing capacity of ABT-229 may have contributed to the failure of ABT-229 in clinical trials..

L19 ANSWER 27 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2002003790 MEDLINE
DOCUMENT NUMBER: 21624129 PubMed ID: 11753157
TITLE: Erythromycin as a prokinetic agent.
COMMENT: Comment on: J Pediatr Gastroenterol Nutr. 2002 Jan;34(1):16-22
Comment on: J Pediatr Gastroenterol Nutr. 2002 Jan;34(1):23-5
AUTHOR: Kaul Ajay
SOURCE: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, (2002 Jan) 34 (1) 13-5.
Journal code: 8211545. ISSN: 0277-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020503
Entered Medline: 20020502

L19 ANSWER 28 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 8
ACCESSION NUMBER: 2003-093333 [08] WPIDS
DOC. NO. CPI: C2003-023568
TITLE: New 1-(2-acylamino-propionyl)-4-(amino or aminoalkyl)-piperidine derivatives, are motilin agonists useful for treating gastro-intestinal motility disorders.
DERWENT CLASS: B02 B03
INVENTOR(S): ANTEL, J; BRUECKNER, R; EICKELMANN, P; JASSERAND, D; PREUSCHOFF, U; SANN, H; WURL, M
PATENT ASSIGNEE(S): (SOLV) SOLVAY PHARM GMBH
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002092592	A1	20021121	(200308)*	GE	37

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002092592	A1	WO 2002-EP4904	20020504

PRIORITY APPLN. INFO: US 2001-291935P 20010521; DE 2001-10122603 20010510
AN 2003-093333 [08] WPIDS
AB WO 200292592 A UPAB: 20030204
NOVELTY - 1-(2-acylamino-3-(hetero)aryl-propionyl)-4-(substituted amino or aminoalkyl)-piperidine derivatives (I) are new. Also new are unsubstituted amino compound intermediates (II).

DETAILED DESCRIPTION - Piperidine derivatives of formula (I) and their acid addition salts are new.

R1 = -A-R'1, 1-6C alkyl (optionally substituted (os) by COOH, OH, =O, =NOH, lower alkoxyimino, NH2, mono- or di-(lower alkyl)-amino or alkoxy) or 3-6C cycloalkyl;

A = direct bond or 1-4C alkylene;

R'1 = phenyl (os by lower alkylenedioxy or by 1-3 of halo, CF3, lower alkyl or lower alkoxy) or heteroaryl (os by halo, lower alkyl or lower alkoxy);

R2 = 1-8C alkyl, naphthyl-lower alkyl, fluorenyl-lower alkyl or -A-R'2;

R'2 = phenyl (os by lower alkylenedioxy or by 1-3 of CF3, lower alkyl, di-(lower alkyl)-amino, lower alkoxy or -O-A-R''2);

R''2 = phenyl (os by lower alkyl, lower alkoxy and/or lower alkylenedioxy);

R3 = H, lower alkyl, naphthyl-lower alkyl, fluorenyl-lower alkyl or -A-R'3;

R'3 = phenyl (os by lower alkylenedioxy or by 1 or 2 of lower alkyl, di-(lower alkyl)-amino, lower alkoxy or -O-A-R''3);

R''3 = phenyl (os by lower alkyl or lower alkoxy);

Ar = phenyl or naphthyl (both os by lower alkylenedioxy or by 1-3 of halo, lower alkyl or lower alkoxy); or indolyl (os by halo, lower alkyl or lower alkoxy);

n = 0-3.

INDEPENDENT CLAIMS are also included for:

(1) the preparation of (I); and

(2) new piperidine derivative intermediates of formula (II).

ACTIVITY - Laxative; Digestive; Antiinflammatory.

MECHANISM OF ACTION - Motilin agonist. In tests using human GPR38 **motilin receptors** expressed in chinese hamster ovary (CHO) cells, N-((1R)-2-(4-(4-isopropylbenzylamino)-1-piperidinyl)-1-(1H-indol-3-ylmethyl)-2-oxoethyl)-3-phenylpropanamide (Ia) at a concentration of 10 micro M gave at least 60% of the degree of stimulation induced by motilin.

USE - (I) stimulate gastrointestinal motility, increase the tone of the lower sphincter of the esophagus and accelerate gastric evacuation. They are useful for treating diseases associated with gastrointestinal motility disorders and/or esophagal reflux, such gastric evacuation deficiency and gastro-esophageal reflux (e.g. induced by diabetic or other gastroparesis), dyspepsia, colon motility anomalies (e.g. irritable bowel syndrome or post-operative motility disorders such as ileus) and gall bladder evacuation disorders. (I) may also show activity on **motilin receptors** in other parts of the body, e.g. the central nervous system.

ADVANTAGE - (I) have a motilin-like beneficial action on the gastrointestinal tract and (unlike prior art motilin agonists, e.g. as described in EP550895-B1) do not have a macrolide structure.

Dwg.0/0

L19 ANSWER 29 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 9

ACCESSION NUMBER: 2002-591245 [63] WPIDS

DOC. NO. CPI: C2002-167407

TITLE: Preparation of a tripeptide derivative by reacting protected amino acid and valine compound, N-methylating, reacting with amino acid and deprotecting.

DERWENT CLASS: B04 B05

INVENTOR(S): JEON, G H; KIM, D I; KIM, S J

PATENT ASSIGNEE(S): (CHUS) CHUGAI PHARM CO LTD; (CHUS) CHUGAI SEIYAKU KK

COUNTRY COUNT: 100

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002064623	A1	20020822	(200263)*	JA	40

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ

NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW
KR 2002066476 A 20020819 (200310)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002064623 A1		WO 2002-JP1139	20020212
KR 2002066476 A		KR 2001-6673	20010212

PRIORITY APPLN. INFO: KR 2001-6673 20010212
AN 2002-591245 [63] WPIDS
AB WO 200264623 A UPAB: 20021001
NOVELTY - Preparation of a tripeptide derivative (I) comprises:
(i) reacting a protected amino acid (II) with a valine compound (III) to give a dipeptide (IV);
(ii) N-methylating (IV) to give a dipeptide (V);
(iii) reacting (V) with an amino acid (VI) to give a tripeptide (VII); and
(iv) removing the amino protecting group.
DETAILED DESCRIPTION - Preparation of a tripeptide derivative of formula (I) comprises:
(i) reacting a protected amino acid of formula (II) with a valine compound of formula (III) to give a dipeptide of formula (IV);
(ii) N-methylating (IV) and if necessary converting R4 to H to give a dipeptide of formula (V);
(iii) reacting (V) with an amino acid of formula (VI) to give a tripeptide of formula (VII); and
(iv) removing the amino protecting group.
R1, R2 = H or 1-4C alkyl;
R3 = halo;
Pr = amino protecting group; and
R4 = H, alkali metal or ester residue as protecting group.
ACTIVITY - Gastrointestinal.
MECHANISM OF ACTION - **Motilin receptor** antagonists
USE - The method is useful for preparing tripeptide derivatives useful as **motilin receptor** antagonists for treating and preventing gastric or intestinal disorders.
ADVANTAGE - Process is industrially advantageous and gives (I) readily in high yields.
Dwg.0/0

L19 ANSWER 30 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 10
ACCESSION NUMBER: 2002-682711 [73] WPIDS
DOC. NO. CPI: C2002-192573
TITLE: Evaluating therapeutic efficacy of compounds, particularly motilide compounds useful as G-protein coupled receptor agonists by determining potency and desensitization values against G-protein coupled receptor and comparing values.
DERWENT CLASS: B02 B04
INVENTOR(S): CARRERAS, C; DILLON, S
PATENT ASSIGNEE(S): (CARR-I) CARRERAS C; (DILL-I) DILLON S; (KOSA-N) KOSAN BIOSCIENCES INC
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002064092	A2	20020822	(200273)*	EN	57
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2002192709	A1	20021219	(200303)		
EP 1365726	A2	20031203	(200380)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002064092	A2	WO 2002-US4462	20020215
US 2002192709	A1 Provisional	US 2001-269631P	20010215
		US 2002-77461	20020215
EP 1365726	A2	EP 2002-714906	20020215
		WO 2002-US4462	20020215

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1365726	A2 Based on	WO 2002064092

PRIORITY APPLN. INFO: US 2001-269631P 20010215; US 2002-77461 20020215

AN 2002-682711 [73] WPIDS

AB WO 200264092 A UPAB: 20021120

NOVELTY - Evaluating the therapeutic efficacy of compounds having agonist activity against a G-protein coupled receptor (GPCR) comprises determining potency and desensitization values for a test compound against GPCR and comparing the potency value with the desensitization value.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a cell line expressing a gene for a synthetic **motilin receptor** and a gene for aequorin;

(2) screening for agonists of a **motilin receptor** which comprises contacting a test compound with a cell expressing a gene for a **motilin receptor** and a gene for aequorin;

(3) evaluating the therapeutic efficacy or usefulness of a motilide having agonist activity against a **motilin receptor** which comprises determining a desensitization value for the motilide against the **motilin receptor**, and

(4) new motilide compounds of formula (I) having a desensitization value against the **motilin receptor** that is greater than the potency value against the **motilin receptor**, preferably at least 10 or at least 100 times the potency value.

W = O or NR;

R = H, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, aryl, alkylaryl, alkenylaryl or alkynylaryl;

R0 = OH or OMe;

R1 = H, OH, halo, NH2, OR9, OC(O)R9, OC(O)NR10R11, NC(O)R9 or NC(O)NR10R11;

R9 = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, 2-10C alkenyl, aryl or heteroaryl;

R10, R11 = H, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl or aryl;

R2, R3 = H, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, aryl, alkylaryl, alkenylaryl or alkynylaryl, or

R2 + R3 = cycloalkyl or cycloaryl;
R4 = H or methyl;
R5 = H, OH or oxo;
R6 = OH or OR12;
R12 = 1-10C alkyl, 2-10C alkenyl or 2-10C alkynyl, and
R7 = methyl, 3-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, alkylaryl, alkenylaryl, alkynylaryl, amidoalkylaryl, amidoalkenylaryl or amidoalkynylaryl.

ACTIVITY - Antiinflammatory; Dermatological; Laxative; Anorectic; Antiemetic.

MECHANISM OF ACTION - G-protein coupled receptor agonist.

Tests are described, but no results are given in the source material.

USE - Used for evaluating the therapeutic efficacy of compounds, particularly motilides including ABT-229 and EM-574 having agonist activity against GPCR. The agonists are used for the treatment of gastroparesis, gastroesophageal reflux disease, anorexia, gall bladder stasis, postoperative paralytic ileus, scleroderma, intestinal pseudoobstruction, gastritis, emesis, and chronic constipation (colonic inertia).

ADVANTAGE - The method evaluates compounds that better correlate with the therapeutic efficiency than evaluating compounds based on potency alone. The methods use efficacy index to evaluate the test compounds minimizing the risk of failure from lack of clinical or therapeutic efficacy. The method evaluates both the new motilide compounds as well as those currently being studied in clinical trials.

Dwg.0/5

L19 ANSWER 31 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 11

ACCESSION NUMBER: 2002-425642 [45] WPIDS
DOC. NO. CPI: C2002-120485
TITLE: New cyclic peptide derivatives, useful as **motilin receptor** antagonists for treating or preventing irritable bowel syndrome, ulcerative colitis, obesity, bacterial diarrhea or diabetes.
DERWENT CLASS: B03 B04
INVENTOR(S): MATSUOKA, H; SATO, T
PATENT ASSIGNEE(S): (CHUS) CHUGAI SEIYAKU KK; (MATS-I) MATSUOKA H; (SATO-I) SATO T
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002016404	A1	20020228	(200245)*	JA	89
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001080120	A	20020304	(200247)		
EP 1312612	A1	20030521	(200334)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2003191053	A1	20031009	(200367)		
JP 2002521499	X	20031007	(200368)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002016404	A1	WO 2001-JP7213	20010823
AU 2001080120	A	AU 2001-80120	20010823
EP 1312612	A1	EP 2001-958426	20010823

	WO 2001-JP7213	20010823
US 2003191053 A1	WO 2001-JP7213	20010823
	US 2003-362574	20030224
JP 2002521499 X	WO 2001-JP7213	20010823
	JP 2002-521499	20010823

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001080120 A	Based on		WO 2002016404
EP 1312612	A1	Based on	WO 2002016404
JP 2002521499 X	Based on		WO 2002016404

PRIORITY APPLN. INFO: JP 2000-253950 20000824
AN 2002-425642 [45] WPIDS
AB WO 200216404 A UPAB: 20020717
NOVELTY - Cyclic peptide derivatives (I) are new.
DETAILED DESCRIPTION - Cyclic peptide derivatives of formula (I) and their salts and hydrates are new:
R1 = phenyl or heterocycle (both optionally substituted);
R2 = H or amino (optionally substituted);
R3-R5 = H, Me or Et;
R6 = H, Me, Et or COR7;
R7 = H or 1-3C alkyl;
V-Z' = CO or CH2;
m = 0 - 2; and
n = 0 - 3.
Provided that when R1 is phenyl, R2 is amino, R3-R6 are H, V is CH2 and W-Z are CO, then m and n are not 1.
INDEPENDENT CLAIMS are also included for intermediates of formula (II)-(IV).
P2 = H or hydroxy protecting group;
P3, P6 = H or carboxy protecting group;
P4, P5, P7 = H or amino protecting group; and
R21 = H or amino (optionally protected and optionally substituted).
ACTIVITY - Antiinflammatory; Gastrointestinal; Antiulcer; Antidiabetic; Anorectic; Antibacterial; Antidiarrheic.
No biological data available.
MECHANISM OF ACTION - **Motilin receptor** antagonist.
In assays (2S-(2S,12S))-2-amino-N-2-(3-t-butyl-4-hydroxyphenylmethyl)-1,4,8-triaza-3,7,13-trioxocyclotridecan-12-yl)-3-(4-fluorophenyl)-N-methylpropionamide (Ia) had an IC50 value for **motilin receptor** binding of 0.53 nM.
USE - (I) are used as **motilin receptor** antagonists useful for treating and preventing, e.g. irritable bowel syndrome, Crohn's disease, ulcerative colitis, pancreatitis, diabetes, obesity, malabsorption syndrome, bacterial diarrhea, atrophic colitis and gastric stasis.
Dwg.0/0

L19 ANSWER 32 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 12

ACCESSION NUMBER:	2003-383123 [37] WPIDS
CROSS REFERENCE:	2003-093333 [08]
DOC. NO. CPI:	C2003-101957
TITLE:	New 1-amidocarbonylmethyl-piperidine derivatives, useful for treating gastrointestinal motility disorders and gastro-esophageal reflux, are motilin agonists.
DERWENT CLASS:	B02 B03
INVENTOR(S):	ANTEL, J; BRUECKNER, R; EICKELMANN, P; JASSERAND, D; PREUSCHOFF, U; SANN, H; WURL, M
PATENT ASSIGNEE(S):	(SOLV) SOLVAY PHARM GMBH
COUNTRY COUNT:	1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 10122603	A1	20021114	(200337)*		11

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 10122603	A1	DE 2001-10122603	20010510

PRIORITY APPLN. INFO: DE 2001-10122603 20010510
AN 2003-383123 [37] WPIDS
CR 2003-093333 [08]
AB DE 10122603 A UPAB: 20030612
NOVELTY - N-Substituted 4-(Amino or aminoalkyl)-1-amidocarbonylmethyl-piperidine derivatives (I) are new.

DETAILED DESCRIPTION - Piperidine derivatives of formula (I) and their acid addition salts are new.

R1 = phenyl or phenylalkyl (both optionally substituted (os) in the ring by alkylenedioxy or 1-3 of halo, CF3, alkyl or alkoxy); heteroaryl or heteroarylalkyl (both os in the ring by halo, alkyl or alkoxy); 1-6C alkyl (os by COOH, OH, =O, =NOH, alkoxyimino, NH2, mono or dialkylamino or alkoxy); or 3-6C cycloalkyl;

R2 = 1-8C alkyl, naphthylalkyl or fluorenylalkyl; or phenyl or phenylalkyl (both os in the ring by alkylenedioxy or 1-3 of CF3, alkyl, dialkylamino or alkoxy, or phenoxy or phenylalkoxy (both os in the ring by alkyl, alkoxy or alkylenedioxy));

R3 = H, alkyl, naphthylalkyl or fluorenylalkyl; or phenyl or phenylalkyl (both os in the ring by alkylenedioxy or 1 or 2 of alkyl, dialkylamino or alkoxy, or phenoxy or phenylalkoxy (both os in the ring by alkyl or alkoxy));

Ar = phenyl or naphthyl (both os by alkylenedioxy or 1-3 of halo, alkyl or alkoxy); or indolyl (os by halo, alkyl or alkoxy); and n = 0-3.

alkyl or alkylene moieties have 1-4C unless specified otherwise.

INDEPENDENT CLAIMS are included for:

(1) preparation of (I); and

(2) new primary amine intermediates of formula (II).

ACTIVITY - Laxative; Antiemetic; Antidiabetic; Antiinflammatory;

MECHANISM OF ACTION - Motilin agonist. N-((1RS)-2-(4-((4-Isopropylbenzyl)-amino)-1-piperidinyl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl)-3-phenyl-propionamide (Ia) at a concentration of 10 micro M caused a degree of stimulation of human GPR38-**motilin receptors** of at least 60% of that caused by motilin.

USE - (I) are used as medicaments, specifically for the treatment and/or prophylaxis of gastrointestinal motility disorders and/or gastro-esophageal reflux (claimed). Typically (I) are useful for treating gastric evacuation disorders due to gastroparesis of various origins (e.g. diabetic gastroparesis), dyspepsia, colon motility disorders (e.g. due to irritable bowel syndrome), post-operative motility disorders (e.g. ileus) or gall bladder evacuation disorders.

ADVANTAGE - (I) are selective motilin agonists which have a motilin-like beneficial effect on gastrointestinal motility and stengthen the tone of the lower esophageal sphincter. Unlike the prior art motilin agonists described in EP550895-B1, (I) do not have a macrocyclic basic structure derived from erythromycin.

Dwg.0/0

L19 ANSWER 33 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:476582 BIOSIS
DOCUMENT NUMBER: PREV200200476582
TITLE: Cyclohexene derivatives useful as antagonists of the

motilin receptor.
AUTHOR(S): Chen, Robert H. [Inventor, Reprint author]; Xiang, Min A. [Inventor]
CORPORATE SOURCE: Belle Mead, NJ, USA
ASSIGNEE: Ortho McNeil-Pharmaceutical, Inc.., Raritan, NJ, USA
PATENT INFORMATION: US 6423714 July 23, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 23, 2002) Vol. 1260, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002
AB The compounds of formula I are useful in treating gastrointestinal disorders associated with antagonizing the **motilin receptor.** The compounds compete with erythromycin and motilin for the **motilin receptor.** In addition the compounds are antagonists of the contractile smooth muscle response to those ligands.

L19 ANSWER 34 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:348268 BIOSIS
DOCUMENT NUMBER: PREV200200348268
TITLE: Cyclopentene compounds useful as antagonists of the **motilin receptor.**
AUTHOR(S): Chen, Robert H. [Inventor]; Xiang, Min A. [Inventor]
CORPORATE SOURCE: ASSIGNEE: Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, USA
PATENT INFORMATION: US 6392040 May 21, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 21, 2002) Vol. 1258, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jun 2002
Last Updated on STN: 19 Jun 2002
AB The compounds of formula I are useful in treating gastrointestinal disorders associated with antagonizing the **motilin receptor.** The compounds compete with erythromycin and motilin for the **motilin receptor.** In addition the compounds are antagonists of the contractile smooth muscle response to those ligands.

L19 ANSWER 35 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:334663 BIOSIS
DOCUMENT NUMBER: PREV200200334663
TITLE: Cyclobutene derivatives useful as antagonists of the **motilin receptor.**
AUTHOR(S): Chen, Robert H. [Inventor, Reprint author]; Xiang, Min A. [Inventor]
CORPORATE SOURCE: Belle Mead, NJ, USA
ASSIGNEE: Ortho-McNeil Pharmaceutical, Inc.
PATENT INFORMATION: US 6384031 May 07, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jun 2002
Last Updated on STN: 12 Jun 2002
AB The compounds of formula I are useful in treating gastrointestinal disorders associated with antagonizing the **motilin receptor.** The compounds compete with erythromycin and motilin for

the **motilin receptor.** In addition the compounds are antagonists of the contractile smooth muscle response to those ligands.

L19 ANSWER 36 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-599577 [64] WPIDS
DOC. NO. CPI: C2002-169401
TITLE: New macrolide compounds useful in the treatment of impaired gastrointestinal motility disorders e.g. gastroparesis are **motilin receptor** competitive binders.
DERWENT CLASS: B02
INVENTOR(S): ASHLEY, G; METCALF, B; SANTI, D; TIAN, Z
PATENT ASSIGNEE(S): (ASHL-I) ASHLEY G; (METC-I) METCALF B; (SANT-I) SANTI D; (TIAN-I) TIAN Z; (KOSA-N) KOSAN BIOSCIENCES INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002051855	A2	20020704	(200264)*	EN	78
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZM ZW					
US 2002094962	A1	20020718	(200264)		
EP 1337540	A2	20030827	(200357)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002051855	A2	WO 2001-US43963	20011121
US 2002094962	A1 Provisional	US 2000-250640P	20001201
	Provisional	US 2001-269632P	20010215
		US 2001-990554	20011121
EP 1337540	A2	EP 2001-995209	20011121
		WO 2001-US43963	20011121

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1337540	A2 Based on	WO 2002051855

PRIORITY APPLN. INFO: US 2001-269632P 20010215; US 2000-250640P 20001201; US 2001-990554 20011121
AN 2002-599577 [64] WPIDS
AB WO 200251855 A UPAB: 20021007
NOVELTY - Macrolide compounds are new.
DETAILED DESCRIPTION - Macrolide compounds of formula (I), (II), (III), (IV), (V), (VI) and (VII) are new.
R6 = H, OH or OR12;
R12 = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl (all optionally substituted);
R = T or H;
T = (alkyl)aryl, alkenylaryl, alkynylaryl (all optionally substituted) or R12;
R' = OH or OCH3;
R1 = H, OH, halide, NH2, OR9, OC(=O)R9, OC(=O)NR10R11, NC(=O)R9 or NC(=O)NR10R11;
R9 = T;

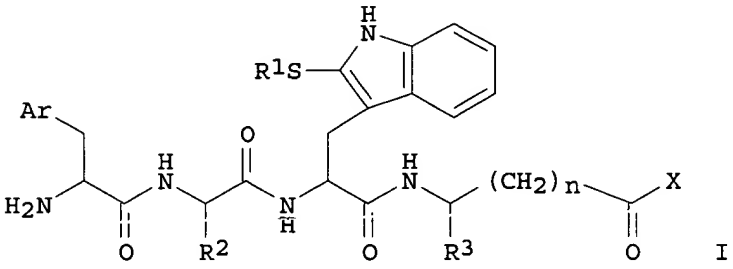
R10, R11 = R;
R2, R3 = R;
R2+R3 = cycloalkyl or aryl;
R4 = H or CH3;
R5 = OH or oxo;
R7 = 2-10C alkenyl, 2-10C alkynyl, (alkyl)aryl, alkenylaryl or alkynylaryl (all optionally substituted), methyl, unsubstituted 3-10C alkyl or substituted 1-10C alkyl;
R8 = alkylaryl, alkenylaryl, alkynylaryl (all optionally substituted) or R12;
X = single or double bond;
Y = R or optionally substituted cladinose;
R13 = alkylaryl, alkenylaryl or alkynylaryl (all optionally substituted), H or R12;
R17 = H or CH3;
R'11 = H, methyl, ethyl, propyl, isopropyl, phenyl or benzyl (not shown in the formula (IV) - (VII));
R11 = H or OH;
R'3 = methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec- butyl or tert-butyl;
R'7 = methyl, vinyl, propyl, isobutyl, pentyl, prop-2-enyl, propargyl, but-3-enyl, 2-azidoethyl, 2-fluoroethyl, 2-chloroethyl, cyclohexyl, phenyl or benzyl; and
R'18 = methyl, ethyl vinyl, propyl, isobutyl, pentyl, prop-2-enyl, propargyl, but-3-enyl, 2-azidoethyl, 2-fluoroethyl, 2-chloroethyl, cyclohexyl, phenyl or benzyl.
ACTIVITY - Dermatological; Antiinflammatory; Antidepressant; Laxative.
MECHANISM OF ACTION - **Motilin receptor** competitive binder.
Test details are described, but no results are given.
USE - In the treatment of gastrointestinal motility disorders (claimed) e.g. gastroparesis, gastroesophageal reflux disease, anorexia, gall bladder stasis, postoperative paralytic ileus, scleroderma, intestinal psuedoobstruction, gastritis, emesis, and chronic constipation (colonic inertia); as prokinetic agents. In the field of chemistry, medicinal chemistry, medicine, molecular biology and pharmacology.
ADVANTAGE - The compounds exhibit superior pharmacological and pharmacokinetic properties.
Dwg.0/0

L19 ANSWER 37 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:575096 CAPLUS
DOCUMENT NUMBER: 137:125397
TITLE: Preparation of peptide derivatives having smooth muscle contracting effect
INVENTOR(S): Haramura, Masayuki; Tsuzuki, Kouichi; Okamachi, Akira; Murayama, Eigoro
PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002059141	A1	20020801	WO 2002-JP557	20020125

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,

TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: JP 2001-17594 A 20010125
OTHER SOURCE(S): MARPAT 137:125397
GI



I

AB (alkylthio)tetrapeptide derivs. represented by the general formula [I; n = an integer of 0 to 6; Ar = an aromatic ring which may have one or more substituents or be fused with another ring; R1 = linear or branched lower alkyl which may be substituted; R2 = linear or branched lower alkyl which may be substituted; R3 = linear or branched lower alkyl which may be substituted; X = amino, hydroxyl, or lower alkoxy] are prepared These peptides are alkylthio derivs. of N-terminus tetrapeptide of motilin which enhance the smooth muscle contracting effect of motilin and possess binding activity for **motilin receptor** (MTL-R) and motilin agonist activity and are useful for treating motilin-related diseases. Thus, 0.592 g H-Phe-Val-Trp-Ile-NH2 was added to a solution of di-Pr disulfide in CF3CO2H, followed by adding CF3SO3Ag, and the resulting mixture was stirred at room temperature for 120 h to give 47% H-Phe-Val-Trp(2'-SCH2CH2Me)-Ile-NH2 (II). II showed IC50 of 0.23 μM for inhibiting the binding of 125I-pMTL to homogenized smooth muscle tissue preparation from upper small intestine of male Japanese white rabbit.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 38 OF 391 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2002165731 MEDLINE
DOCUMENT NUMBER: 21895803 PubMed ID: 11781320
TITLE: Differential determinants for peptide and non-peptidyl ligand binding to the **motilin receptor.** Critical role of second extracellular loop for peptide binding and action.
AUTHOR: Matsuura Bunzo; Dong Maoqing; Miller Laurence J
CORPORATE SOURCE: Center for Basic Research in Digestive Diseases, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Mar 22) 277 (12) 9834-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020319
Last Updated on STN: 20030105
Entered Medline: 20020429
AB The predicted second extracellular loop domain of the **motilin receptor** is of particular interest because it is a region that is

quite distinct from the analogous regions in other family members that are most closely related and because the initial report of the photoaffinity labeling of a domain of this receptor included this region (Coulie, B. J., Matsuura, B., Dong, M., Hadac, E. M., Pinon, D. I., Feighner, S. D., Howard, A. D., and Miller, L. J. (2001) J. Biol. Chemical 276, 35518-35522). In the current work, **motilin receptor** constructs were prepared that included sequential deletions ranging from single residues to twelve amino acid segments throughout this 67 amino acid domain. Each construct was expressed in COS cells and characterized for motilin radioligand binding and motilin-stimulated intracellular calcium responses. The only segments that had negative impact on motilin binding and biological activity included deletion constructs DeltaCys(235), Delta179-182, and Delta241-246. Cys(235) is likely involved in the highly conserved and functionally important disulfide bond linking the first and second loops of G protein-coupled receptors. Alanine replacements for each of the amino acid residues in the other two segments revealed that the perimembranous residues at both ends of this loop, Val(179) and Leu(245) and Arg(246), were responsible for the negative impact on motilin binding and biological activity. Of note, these mutants responded normally to the non-peptidyl agonist, erythromycin. These data support important functional roles for both amino-terminal and carboxyl-terminal perimembranous regions of the second loop for responses to the natural agonist peptide, while supporting independent determinants for action of a non-peptidyl agonist ligand.

L19 ANSWER 39 OF 391 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2002419852 MEDLINE
DOCUMENT NUMBER: 21934712 PubMed ID: 11937338
TITLE: Design and synthesis of novel tetra-peptide motilin agonists.
AUTHOR: Haramura Masayuki; Tsuzuki Kouichi; Okamachi Akira; Yogo Kenji; Ikuta Makoto; Kozono Toshiro; Takanashi Hisanori; Murayama Eigoro
CORPORATE SOURCE: Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co. Ltd., 1-135 Komakado, Gotemba, 412-8513, Shizuoka, Japan.. mharamura@chugaibio.com
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY, (2002 Jun) 10 (6) 1805-11.
Journal code: 9413298. ISSN: 0968-0896.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20020815
Last Updated on STN: 20030211
Entered Medline: 20030210

AB A series of novel tetra-peptide motilin agonists, having the general structure H-Phe-Val-X-Ile-NH(2), were designed, on the basis of structure-activity relationship studies of motilin. Peptides, in which X is a side chain substituted tryptophan residue, have agonistic activity. H-Phe-Val-Trp(2'-CH(2)CH(2)OH)-Ile-NH(2)(7), H-Phe-Val-Trp(2'-SCH(3))-Ile-NH(2)(8), and H-Phe-Val-Trp(2'-SCH(2)CH(2)CH(3))-Ile-NH(2)(9), showed an EC(50) for contractile activity in the rabbit smooth muscle of 14.1+/-3.2, 12.9+/-4.1, and 4.6+/-1.6 microM, respectively. Interaction of the tryptophan aliphatic side chain with **motilin receptor** appears to influence the signal transduction via **motilin receptor.**

L19 ANSWER 40 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2002644975 MEDLINE
DOCUMENT NUMBER: 22291669 PubMed ID: 12404232
TITLE: Motilin regulates interdigestive gastric blood flow in dogs.
AUTHOR: Jin Chunxiang; Naruse Satoru; Kitagawa Motoji; Ishiguro

Hiroshi; Muxin Wei; Nakajima Morio; Yokohata Koji; Ito Osamu; Hayakawa Tetsuo
CORPORATE SOURCE: Internal Medicine II, Nagoya University School of Medicine, Nagoya, Japan.
SOURCE: GASTROENTEROLOGY, (2002 Nov) 123 (5) 1578-87.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021030
Last Updated on STN: 20021217
Entered Medline: 20021209

AB BACKGROUND & AIMS: Gastric blood flow exhibits cyclical increases in phase with the interdigestive contractions and secretion of the stomach in dogs. The aim of this study is to clarify the regulatory role of motilin in interdigestive gastric blood flow in dogs. METHODS: Blood flow of the left gastric (LGA) and superior mesenteric (SMA) arteries were measured by ultrasound transit-time blood-flow meters in 5 conscious dogs. Motilin was infused intravenously with or without Phe-cyclo[Lys-Tyr(3-tBu)-betaAla-]. trifluoroacetate (GM-109; motilin antagonist), granisetron (5-HT3 antagonist), atropine, hexamethonium (C6), phenoxybenzamine, propranolol, or cimetidine. RESULTS: Motilin (12.5, 25, 50, and 100 pmol x kg(-1) x h(-1)) induced LGA blood-flow responses, consisting of a sustained increase and a rapid phasic change coupled with a contraction, without affecting the blood pressure, heart rate, and SMA blood flow. GM-109 completely abolished the LGA, motility, and secretory responses to motilin (100 pmol x kg(-1) x h(-1)). Atropine abolished motilin-induced gastric contractions, secretion, and phasic changes of LGA blood flow but failed to affect the sustained flow increase. However, atropine partially inhibited the LGA responses to lower doses of motilin. The LGA flow responses to motilin were not inhibited by granisetron, C6, alpha-adrenergic, beta-adrenergic, or H2 blockers. Motilin induced significantly larger gastric vasodilatation than the equivalent doses of VIP. CONCLUSIONS: Motilin has a potent and selective gastric vasodilator effect, which appears to be mediated by both cholinergic and noncholinergic mechanisms. Motilin plays an important role in the regulation of interdigestive gastric blood flow in dogs.

L19 ANSWER 41 OF 391 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2002668061 MEDLINE
DOCUMENT NUMBER: 22315701 PubMed ID: 12428665
TITLE: Binding of radiolabeled porcine motilin and erythromycin lactobionate to smooth muscle membranes in various segments of the equine gastrointestinal tract.
AUTHOR: Koenig Judith B; Cote Nathalie; LaMarre Jonathan; Harris William H; Trout Donald R; Kenney Daniel G; Monteith Gabrielle
CORPORATE SOURCE: Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Canada.
SOURCE: AMERICAN JOURNAL OF VETERINARY RESEARCH, (2002 Nov) 63 (11) 1545-50.
Journal code: 0375011. ISSN: 0002-9645.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021114
Last Updated on STN: 20030321
Entered Medline: 20030320

AB OBJECTIVE: To identify and characterize **motilin receptors** in equine duodenum, jejunum, cecum, and large colon and to determine whether erythromycin lactobionate competes with porcine

motilin for binding to these receptors. SAMPLE POPULATION: Specimens of various segments of the intestinal tracts of 4 adult horses euthanatized for reasons unrelated to gastrointestinal tract disease. PROCEDURE: Cellular membranes were prepared from smooth muscle tissues of the duodenum, jejunum, pelvic flexure, and cecum. Affinity and distribution of motilin binding on membrane preparations were determined by use of 125I-labeled synthetic porcine motilin. Displacement studies were used to investigate competition between 125I-labeled synthetic porcine motilin and erythromycin lactobionate for binding to **motilin receptors** in various segments of bowel. RESULTS: Affinity of 125I-labeled synthetic porcine motilin for the equine **motilin receptor** was estimated to be 6.1nM. A significantly higher number of **motilin receptors** was found in the duodenum than in the pelvic flexure and cecum. The jejunum had a significantly higher number of **motilin receptors** than the cecum. Erythromycin lactobionate displacement of 125I-labeled porcine motilin from the equine **motilin receptor** did not differ significantly among various segments of bowel. CONCLUSIONS AND CLINICAL RELEVANCE: **Motilin receptors** were found in the duodenum, jejunum, pelvic flexure, and cecum of horses. The highest number of **motilin receptors** was in the duodenum, and it decreased in more distal segments of bowel. Erythromycin lactobionate competed with motilin binding in the equine gastrointestinal tract. This suggests that 1 of the prokinetic actions of erythromycin in horses is likely to be secondary to binding on **motilin receptors**
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L19 ANSWER 42 OF 391 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2002312705 MEDLINE
DOCUMENT NUMBER: 22050119 PubMed ID: 12054506
TITLE: The motilin pharmacophore in CHO cells expressing the human **motilin receptor.**
AUTHOR: Thielemans Leen; Depoortere Inge; Vanden Broeck Jozef; Peeters Theo L
CORPORATE SOURCE: Department of Pathophysiology, Gut Hormone Lab, Center for Gastroenterological Research, Katholieke Universiteit Leuven, Leuven B-3000, Belgium.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2002 May 17) 293 (4) 1223-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020611
Last Updated on STN: 20020629
Entered Medline: 20020628
AB We performed a structure-activity study with the human **motilin receptor**, which was recently cloned from thyroid tissue. N-terminal fragments, Ala-analogs of motilin, and motilides were tested in a cell line that expresses the cloned human **motilin receptor** and apoaequorin. Full potency to induce calcium fluxes was obtained with N-terminal fragments of 14 amino acids. Motilin fragments 1-14 in which residues 1 (Phe), 4 (Ile), and 7 (Tyr) were replaced by Ala showed the largest reduction in potency. Only motilides with an enol configuration had markedly higher potencies compared to erythromycin A. The potencies to induce Ca(2+) fluxes correlated strongly with rabbit binding and contractility data, suggesting that the cloned receptor is indeed the **motilin receptor**, responsible for contractile effects. Conservation of the motilin pharmacophore in evolution indicates an important physiological role of motilin.

L19 ANSWER 43 OF 391 MEDLINE on STN DUPLICATE 17

ACCESSION NUMBER: 2002318359 MEDLINE
DOCUMENT NUMBER: 22028591 PubMed ID: 12032184
TITLE: In vitro evaluation of motilin agonism by macrolide immunosuppressive drugs.
AUTHOR: Van Vlem Bruno; Schoonjans Renaat; Vanholder Raymond; De Vos Martine; Depoortere Inge; Peeters Theo L; Lefebvre Romain
CORPORATE SOURCE: Renal Division, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium..
bruno.vanvlem@rug.ac.be
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (2002 Jun) 17 (6) 973-7.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20020614
Last Updated on STN: 20030111
Entered Medline: 20030110

AB BACKGROUND: The immunosuppressive drugs tacrolimus and sirolimus may have a stimulatory influence on gastric emptying, in view of their macrolide structure. The aim of this study was to investigate in vitro the possible interaction of tacrolimus and sirolimus with **motilin receptors** in the rabbit antrum and duodenum. METHODS: Rabbit duodenum strips were mounted under a load of 1 g in 10 ml organ baths containing Krebs solution. Erythromycin, tacrolimus, cyclosporin, and sirolimus were added to the bathing solution in a cumulative way; in a second series, after incubation with cyclosporin (10(-7) mol/l), tacrolimus (10(-8) mol/l), or sirolimus (3 x 10(-8) mol/l), a cumulative concentration-response curve to erythromycin was obtained. The effect of cumulatively added tacrolimus and nle(13)-porcine motilin on the contractile response to electrical field stimulation was tested in strips from the rabbit gastric antrum. Displacement by tacrolimus of (125)I-nle(13)-porcine motilin bound to its receptor was tested with crude homogenates of the smooth-muscle layer of the rabbit antrum. RESULTS: In rabbit duodenum strips, carbachol (10(-5) mol/l) induced a stable and reproducible contraction. Erythromycin induced concentration-dependent contractions. Expressed as a percentage of the response to carbachol, the maximal attained effect was 78%; the EC(50) was 4.8 x 10(-7) mol/l. Tacrolimus (10(-8) to 10(-5) mol/l), cyclosporin (10(-8) to 10(-5) mol/l), and sirolimus (10(-8) to 3 x 10(-5) mol/l) had no influence. The response to erythromycin (10(-8) to 3 x 10(-5) mol/l) in the presence of cyclosporin (10(-7) mol/l), tacrolimus (10(-8) mol/l), or sirolimus (3 x 10(-8) mol/l) did not differ from that obtained with erythromycin alone, except for a decrease of the EC(50) in the presence of tacrolimus (2.2 x 10(-7) mol/l) ($P<0.05$ vs erythromycin alone). Motilin enhanced the response to electrical field stimulation of rabbit antral strips, but tacrolimus had no stimulatory effect. Tacrolimus weakly displaced motilin bound to its receptor. The pIC(50) was 4.97. CONCLUSIONS: As opposed to erythromycin, neither tacrolimus nor sirolimus showed a contractile effect in the rabbit duodenum. Tacrolimus did not activate the neural **motilin receptor** of the rabbit gastric antrum and had low affinity for the smooth-muscle **motilin receptor.** It is thus unlikely that these macrolide immunosuppressive drugs possess gastroprokinetic effects via motilin agonism.

L19 ANSWER 44 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2002376065 MEDLINE
DOCUMENT NUMBER: 22117040 PubMed ID: 12121143
TITLE: Introduction of lanthanide(III) chelates to oligopeptides on solid phase.
AUTHOR: Peuralahti Jari; Hakala Harri; Mukkala Veli-Matti; Loman Kristiina; Hurskainen Pertti; Mulari Outi; Hovinen Jari

CORPORATE SOURCE: PerkinElmer Life Sciences, Wallac Oy, P.O. Box 10, FIN-20101 Turku, Finland.
SOURCE: BIOCONJUGATE CHEMISTRY, (2002 Jul-Aug) 13 (4) 870-5. Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20020718
Last Updated on STN: 20021212
Entered Medline: 20030805

AB The synthesis of oligopeptide building blocks for the introduction of nonluminescent and luminescent lanthanide(III) chelates to the oligopeptide structure on the solid phase is described. The oligopeptide conjugates synthesized were used in DELFIA-based receptor binding assay (motilin) as well as in LANCE time-resolved fluorescence quenching assay (caspase-3).

L19 ANSWER 45 OF 391 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2002244041 MEDLINE
DOCUMENT NUMBER: 21926702 PubMed ID: 11929393
TITLE: Efficacy of a **motilin receptor** agonist (ABT-229) for the treatment of gastro-oesophageal reflux disease.
AUTHOR: Chen C L; Orr W C; Verlinden M H; Dettmer A; Brinkhoff H; Riff D; Schwartz S; Soloway R D; Krause R; Lanza F; Mack R J
CORPORATE SOURCE: Lynn Institute for Healthcare Research, Oklahoma City, OK 73112, USA.
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (2002 Apr) 16 (4) 749-57. Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020502
Last Updated on STN: 20020907
Entered Medline: 20020906

AB BACKGROUND: ABT-229 is a potent motilin agonist without significant antibiotic activity. It has been shown to improve gastric emptying in humans and to increase lower oesophageal sphincter pressure in cats. AIM: To assess the efficacy of four different doses of ABT-229 (1.25 mg, 2.5 mg, 5 mg, 10 mg b.d.) compared to placebo in the treatment of gastro-oesophageal reflux disease, and to determine its safety in patients with gastro-oesophageal reflux disease. METHODS: In a double-blind, multicentre study, 324 patients with heartburn were randomized to receive four different doses of ABT-229 or placebo for 8 weeks. The efficacy was evaluated by Patient Symptom Questionnaire, daily diary, endoscopy and global evaluation of efficacy. RESULTS: There were no statistically significant improvement scores for any of the ABT-229 treatment groups vs. the placebo group in any of the efficacy parameters. Reflux symptom scores were significantly worse after treatment in the dyspeptic group. ABT-229 appeared to be well tolerated and safe in total daily doses up to 20 mg. CONCLUSION: ABT-229 appears to have limited, if any, clinical utility in the treatment of gastro-oesophageal reflux disease.

L19 ANSWER 46 OF 391 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 2002080968 MEDLINE
DOCUMENT NUMBER: 21666388 PubMed ID: 11806718

TITLE: Design and synthesis of motilin antagonists derived from the [1-4] fragment of porcine motilin.
AUTHOR: Haramura Masayuki; Okamachi Akira; Tsuzuki Kouichi; Yogo Kenji; Ikuta Makoto; Kozono Toshiro; Takanashi Hisanori; Murayama Eigoro
CORPORATE SOURCE: Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co. Ltd., 1-135 Komakado, Gotemba-shi, Shizuoka 412-8513, Japan.. mharamura@chugaibio.com
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (2002 Jan 31) 45 (3) 670-5. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020128
Last Updated on STN: 20020220
Entered Medline: 20020219

AB A series of cyclic peptides having the general structure H-Phe-c[-N(epsilon)-Lys-X-NH-(CH(2))(n)-CO-] were designed on the basis of structure-activity relationship studies of motilin. All were motilin antagonists. The cyclic peptides, in which X is a 3-tert-butyl-substituted tyrosine residue (H-Phe-c[-N(epsilon)-Lys-Tyr(3-tBu)-beta Ala-] (3), H-Phe-c[-N(epsilon)-Lys-Tyr(3-tBu)-Gly-] (6), H-Phe-c[-N(epsilon)-Lys-Tyr(3-tBu)-Abu-] (7), and H-Phe-c[-N(epsilon)-Lys-Tyr(3-tBu)-Ahx-] (8)) showed potent **motilin receptor** antagonistic activity in the rabbit smooth muscle (pA(2) > 7). The 3-tert-butyl Tyr was found to be the moiety responsible for enhanced binding to the **motilin receptor**, while the size of the ring had little importance.

L19 ANSWER 47 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:417644 SCISEARCH
THE GENUINE ARTICLE: 548AW
TITLE: InCHO-K1 cells expressing the **motilin receptor**, the ability of motilides to desensitize the **motilin receptor** is not determined by their potency
AUTHOR: Thielemans L (Reprint); Hoogmartens J; Depoortere I; Peeters T L
SOURCE: GASTROENTEROLOGY, (APR 2002) Vol. 122, No. 4, Supp. [1], pp. A552-A552. MA W1030.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 48 OF 391 EMBASE on STN
ACCESSION NUMBER: 2003250068 EMBASE
TITLE: Chemical genomics, pharmacogenomics and pharmacogenetics.
AUTHOR: Desai M.C.; Greenlee W.J.
CORPORATE SOURCE: M.C. Desai, Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608, United States. manoj_desai@chiron.com
SOURCE: Current Opinion in Drug Discovery and Development, (2002) 5/4 (475-476).
ISSN: 1367-6733 CODEN: CODDFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
039 Pharmacy
LANGUAGE: English

L19 ANSWER 49 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:416159 SCISEARCH
THE GENUINE ARTICLE: 548AW
TITLE: Distinct determinants for **motilin receptor** activation by peptide and non-peptidyl ligands. Critical role of the second extracellular loop for peptide binding and action
AUTHOR: Matsuura B (Reprint); Dong M Q; Onji M; Miller L J
SOURCE: GASTROENTEROLOGY, (APR 2002) Vol. 122, No. 4, Supp. [1], pp. A259-A259. MA M1044.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 50 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:416161 SCISEARCH
THE GENUINE ARTICLE: 548AW
TITLE: **Motilin receptor** desensitization in cell based and contractility assays
AUTHOR: Carreras C W (Reprint); Thijs T; Liu Y; Dillon S B; Peeters T
SOURCE: GASTROENTEROLOGY, (APR 2002) Vol. 122, No. 4, Supp. [1], pp. A259-A259. MA M1046.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 51 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 20
ACCESSION NUMBER: 2002:410630 BIOSIS
DOCUMENT NUMBER: PREV200200410630
TITLE: Design, SAR and pharmacology of GM-611, the first acid-stable nonpeptide **motilin receptor** agonist.
AUTHOR(S): Koga, Hiroshi [Reprint author]; Takanashi, Hisanori; Itoh, Zen; Omura, Satoshi
CORPORATE SOURCE: 1-33-9 Higashi-Omiya, Saitama-shi, Saitama, 330-0021, Japan
SOURCE: Drugs of the Future, (March, 2002) Vol. 27, No. 3, pp. 255-272. print.
ISSN: 0377-8282.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 2002
Last Updated on STN: 31 Jul 2002

L19 ANSWER 52 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:73409 SCISEARCH
THE GENUINE ARTICLE: 511TZ
TITLE: Intestinal absorption and presystemic elimination of the prokinetic agent, EM574, in the rabbit
AUTHOR: Gan G F; Cartier L L; Huang Y; Yang Z; Sawchuk R J (Reprint)
CORPORATE SOURCE: Univ Minnesota, Coll Pharm, Dept Pharmaceut, Minneapolis, MN 55455 USA (Reprint); Bristol Myers Squibb Co, Dept Metab & Pharmacokinet, Wallingford, CT 06492 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF PHARMACEUTICAL SCIENCES, (JAN 2002) Vol. 91,

No. 1, pp. 217-228.
Publisher: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA.
ISSN: 0022-3549.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 25
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The purpose of this study was to characterize the pharmacokinetics and dose proportionality of the prokinetic macrolide, EM574, in rabbits following intravenous dosing, and to determine the intestinal absorption and intestinal and hepatic first-pass elimination of EM574 in rabbits. Two doses (0.05 and 0.25 mg/kg) of EM574 were given to rabbits intravenously in a crossover study. In a separate gut perfusion study, rabbit duodenal or jejunal segments were perfused with EM574 solution at 0.2 mL/min for 130 min. Plasma levels of EM574 were determined by a validated LC-MS/MS assay, and concentrations in perfusate were determined by HPLC with UV detection. The absorptive clearance (PeA) of EM574 was calculated from the steady-state rate of disappearance from the gut lumen during perfusion. The cumulative amount (A(app)) of drug appearing in the systemic circulation was calculated by deconvolution, where the input response was the plasma concentration-time profile during intestinal perfusion and the unit impulse response was the mean profile following intravenous bolus dosing to sham-operated rabbits in a separate experiment. FgFh was calculated from the ratio of A(app) to the total amount disappeared from gut lumen during perfusion. Hepatic first-pass elimination was measured by intraportal venous infusion. EM574 exhibits linear kinetics over the dose range studied. CL, V-ss, and terminal half-life (mean +/- SD) of EM574 were 68.6 +/- 15.5 mL/min/kg, 13.4 +/- 3.0 L/kg, and 2.7 +/- 0.8 h, respectively. EM574 is expected to be absorbed completely from the rabbit small intestine based on its high jejunal PeA values (8.1 +/- 2.2, and 5.5 +/- 1.5 muL/min/cm following low and high dose perfusion, respectively). The first-pass extraction of EM574 was substantial and dose independent. Mean F-g and F-h were 0.14 and 0.20, respectively, suggesting that the intestinal and hepatic first-pass elimination of EM574 were comparable. Deconvolution was successfully applied in the determination of gut wall and hepatic first-pass elimination of EM574. (C) 2002 WileyLiss, Inc. and the American Pharmaceutical Association.

L19 ANSWER 53 OF 391 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 2002053706 MEDLINE
DOCUMENT NUMBER: 21637867 PubMed ID: 11779105
TITLE: Stable expression of a synthetic gene for the human **motilin receptor**: use in an aequorin-based receptor activation assay.
AUTHOR: Carreras Christopher W; Siani Michael A; Santi Daniel V; Dillon Susan B
CORPORATE SOURCE: Department of Pharmacological Sciences, Kosan Biosciences, Inc., 3832 Bay Center Place, Hayward, California 94545, USA.. carreras@kosan.com
SOURCE: ANALYTICAL BIOCHEMISTRY, (2002 Jan 15) 300 (2) 146-51. Journal code: 0370535. ISSN: 0003-2697.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020530
Entered Medline: 20020529

AB A synthetic gene for the human **motilin receptor** containing 33 unique restriction sites was designed and stably coexpressed in HEK293 cells with the bioluminescent Ca(2+) indicator protein aequorin. The dose-dependent response of the receptor to motilin was demonstrated using transient transfections, and a stable cell line was selected.

[(125)I]Motilin binding was used to estimate receptor expression level for the stable cell line, and titration of a membrane preparation indicated a K(d) value of 0.8 nM. The same cell line was used to evaluate a panel of erythromycin-derived agonists and provided EC(50) values for receptor activation that agree closely with data obtained in contractility assays. The peptide antagonist ANQ11125 (Phe3Leu13 motilin 1-14) inhibited motilin induced response with a K(i) value of 10 nM. The system is well-suited for the screening of compound libraries and receptor mutagenesis studies. (c)2001 Elsevier Science.

L19 ANSWER 54 OF 391 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 2002003791 MEDLINE
DOCUMENT NUMBER: 21624130 PubMed ID: 11753158
TITLE: Effect of erythromycin on gastroduodenal contractile activity in developing neonates.
COMMENT: Comment in: J Pediatr Gastroenterol Nutr. 2002 Jan;34(1):13-5
AUTHOR: Jadcherla Sudarshan Rao; Berseth Carol Lynn
CORPORATE SOURCE: Department of Pediatrics and Section of Neonatology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA.. jadcherl@mcw.edu
SOURCE: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, (2002 Jan) 34 (1) 16-22.
Journal code: 8211545. ISSN: 0277-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020503
Entered Medline: 20020502

AB BACKGROUND: The occurrence of phase III of migrating motor complexes in neonates is inversely related to gestational age, and it can be triggered in some infants by the **motilin receptor** agonist erythromycin. After intragastric erythromycin, the authors determined 1) the occurrence and characteristics of phase III of migrating motor complexes, 2) the antral and duodenal motor responses, and 3) the dose-response relation among preterm and full-term infants. METHODS: Using an unbalanced, repeated measures design, 25 preterm and term infants were given two of three doses of intragastric erythromycin: 0.75, 1.5, and 3.0 mg/kg. Motor activity was recorded 3 hours before and 2 hours after each dose using a continuous water perfusion manometry system. RESULTS: Erythromycin failed to induce phase III of migrating motor complexes in infants younger than 31 weeks' gestation; however, it induced phase III in a dose-dependent manner among infants whose gestational ages were 32 weeks and older ($P < 0.05$). Erythromycin significantly increased the amplitude and frequency of antral contractions in term infants and significantly increased the duodenal contraction amplitude in older preterm and term infants, but these effects were absent in younger preterm infants. CONCLUSIONS: The ontogenic emergence of the **motilin receptor**-mediated induction of phase III occurs by 32 weeks' gestation, whereas the non-motilin-mediated response of increased antroduodenal motor activity is not observed until term. Therefore, early use of erythromycin as a prokinetic agent may not be useful in very preterm infants, partially useful in older preterm infants, and useful in full-term infants.

L19 ANSWER 55 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 23
ACCESSION NUMBER: 2002:22815 SCISEARCH
THE GENUINE ARTICLE: 504UE
TITLE: Erythromycin as a prokinetic agent
AUTHOR: Kaul A (Reprint)
CORPORATE SOURCE: Childrens Hosp, Med Ctr, Div Pediat Gastroenterol, 3333

Burnet Ave, Cincinnati, OH 45249 USA (Reprint); Childrens Hosp, Med Ctr, Div Pediat Gastroenterol, Cincinnati, OH 45249 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, (JAN 2002) Vol. 34, No. 1, pp. 13-15.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0277-2116.
DOCUMENT TYPE: Editorial; Journal
LANGUAGE: English
REFERENCE COUNT: 27

L19 ANSWER 56 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:190538 CAPLUS
TITLE: Solution-Phase Synthesis of a Macrolide Combinatorial Library
AUTHOR(S): Tian, Zong-Qiang; Wang, Zhan; Raniwala, Rafiqa; Ashley, Gary W.; Myles, David C.; Metcalf, Brian
CORPORATE SOURCE: Kosan Biosciences, Inc, Hayward, CA, 94545, USA
SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), ORGN-003. American Chemical Society: Washington, D. C.
CODEN: 69CKQP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB We report the design and synthesis of a macrolide combinatorial library based on the erythromycin A (1) scaffold. Macrolides, a class of compds. containing a lactone moiety in a large ring, have been used extensively for treatment of upper and lower respiratory tract infections. Erythromycin A has been in clin. use for the past 40 yr. Antibacterial macrolides function by interacting with bacterial ribosome and inhibiting protein synthesis. Some macrolides and their derivs. have been shown to bind to certain G-protein coupled receptors. For example, the 6,9-enol ether of erythromycin A (2) is a potent agonist for the **motilin receptor** and has been shown to induce GI motility. Macrolides are considered to be very well tolerated and safe. There lies great potential in screening libraries of macrolide to identify new antibacterials and new ligands for GPCR's. In spite of the many uses, reports on combinatorial libraries of macrolides are limited. We will discuss the solution-phase synthesis of a macrolide combinatorial library based on the erythromycin A scaffold.

L19 ANSWER 57 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:380127 BIOSIS
DOCUMENT NUMBER: PREV200300380127
TITLE: ELECTROPHYSIOLOGICAL EFFECTS OF MOTILIN AND ERYTHROMYCIN ON RAT CEREBELLAR PURKINJE NEURONS.
AUTHOR(S): Pang, P. [Reprint Author]; Chen, L. [Reprint Author]; Yung, W. H. [Reprint Author]
CORPORATE SOURCE: Physiology Dept, The Chinese Univsersity of Hong Kong, Shatin, China
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 827.5. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Aug 2003
Last Updated on STN: 20 Aug 2003

AB Motilin, a 22-amino acid gastrointestinal polypeptide first isolated from porcine intestine, promotes gut motility. Radioimmunoassay and immunocytochemistry showed that motilin-like immunoreactivity is widely distributed in the brain. In the cerebellum, motilin is expressed by most Purkinje neurons. Here we applied whole-cell current-clamp and voltage-clamp recordings on rat cerebellar slices to study the electrophysiological effects of motilin and erythromycin, a **motilin receptor** agonist. Under current-clamp recording, superfusion of 10 nM motilin and 100M erythromycin depolarized the majority of Purkinje neurons sampled by 3.90.1 mV (n=4) and 5.00.4mV (n=22) respectively. Some Purkinje neurons, however, did not respond to both compounds. The depolarization, if any, was usually accompanied by a shift of firing pattern from regular to irregular, burst-like firing. Consistent with the current-clamp data, an inward current, persisted in the presence of tetrodotoxin, was induced by erythromycin in a subpopulation of Purkinje neurons (13024pA, n=9). Since the Cs-sensitive hyperplarization-activated current (Ih) was not affected by erythromycin (n=5), the shift in firing mode of Purkinje neurons was unlikely due to modulation of Ih. On the other hand, in the presence of TEA, erythromycin-induced inward current was eliminated (n=3). These data suggest that motilin may be neuroactive in the cerebellum, and that it modulates the activity of Purkinje neurons by blocking a TEA-sensitive K-conductance.

L19 ANSWER 58 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:508361 BIOSIS
DOCUMENT NUMBER: PREV200200508361
TITLE: Expression of motilin, ghrelin and their receptors in the myenteric plexus of guinea pig small intestine.
AUTHOR(S): Xu, Luo [Reprint author]; Depoortere, Inge [Reprint author]; Peeters, Theo [Reprint author]
CORPORATE SOURCE: Leuven, Belgium
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A.54-A.55. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L19 ANSWER 59 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:508359 BIOSIS
DOCUMENT NUMBER: PREV200200508359
TITLE: Molecular, functional and cross-species comparisons between the receptors for the prokinetic neuropeptides, motilin and ghrelin.
AUTHOR(S): Hill, Jeffrey [Reprint author]; Szekeres, Phillip [Reprint author]; Muir, Alison [Reprint author]; Sanger, Gareth J. [Reprint author]
CORPORATE SOURCE: Harlow, Essex, UK
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A.54. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L19 ANSWER 60 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:519273 BIOSIS
DOCUMENT NUMBER: PREV200200519273
TITLE: **Motilin receptor** desensitization in cell based and contractility assays.
AUTHOR(S): Carreras, C. W. [Reprint author]; Thijs, Theo; Liu, Y.; Dillon, S. B.; Peeters, Theo
CORPORATE SOURCE: Hayward, CA, USA
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A-259. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Oct 2002
Last Updated on STN: 9 Oct 2002

L19 ANSWER 61 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:519268 BIOSIS
DOCUMENT NUMBER: PREV200200519268
TITLE: Contractile effects of ghrelin and of the growth-hormone releasing peptide, GHRP-6, in the rabbit antrum.
AUTHOR(S): Depoortere, Inge [Reprint author]; Thielemans, Leen; Robberecht, Patrick; Thijs, Theo; Peeters, Theo
CORPORATE SOURCE: Leuven, Belgium
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A-258. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Oct 2002
Last Updated on STN: 9 Oct 2002

L19 ANSWER 62 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:519271 BIOSIS
DOCUMENT NUMBER: PREV200200519271
TITLE: Distinct determinants for **motilin receptor** activation by peptide and non-peptidyl ligands. Critical role of the second extracellular loop for peptide binding and action.
AUTHOR(S): Matsuura, Bunzo [Reprint author]; Dong, Maoqing; Onji, Morikazu; Miller, Laurence J.
CORPORATE SOURCE: Rochester, MN, USA
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A-259. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Oct 2002
Last Updated on STN: 9 Oct 2002

L19 ANSWER 63 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:531316 BIOSIS

DOCUMENT NUMBER: PREV200200531316
TITLE: Characterization of the new motilin agonist SLV 311.
AUTHOR(S): Sann, Holger [Reprint author]; Depoortere, Inge; Eeckhout, Christian; Becker, Josef; Reiche, Dania; Preuschoff, Ulf; Peeters, Theo L.; Jasserand, Daniel
CORPORATE SOURCE: Hannover, Germany
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A.556. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2002
Last Updated on STN: 16 Oct 2002

L19 ANSWER 64 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:531296 BIOSIS
DOCUMENT NUMBER: PREV200200531296
TITLE: In CHO-K1 cells expressing the **motilin receptor**, the ability of motilides to desensitize the **motilin receptor** is not determined by their potency.
AUTHOR(S): Thielemans, Leen [Reprint author]; Hoogmartens, Jos [Reprint author]; Depoortere, Inge [Reprint author]; Peeters, Theo L. [Reprint author]
CORPORATE SOURCE: Leuven, Belgium
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A.552. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2002
Last Updated on STN: 5 Dec 2002

L19 ANSWER 65 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:530716 BIOSIS
DOCUMENT NUMBER: PREV200200530716
TITLE: Effect of oral clarythromycin on gall bladder motility in humans.
AUTHOR(S): Sengupta, Subhasish [Reprint author]; Schuchardt, Katrin [Reprint author]; Moneley, Daragh [Reprint author]; Baj, Mahesh [Reprint author]; O'Donnell, Luke J. D. [Reprint author]
CORPORATE SOURCE: Castlebar, Ireland
SOURCE: Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A-440. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association. San Francisco, CA, USA. May 19-22, 2002.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Oct 2002
Last Updated on STN: 16 Oct 2002

L19 ANSWER 66 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2001170993 MEDLINE

DOCUMENT NUMBER: 21119517 PubMed ID: 11271453
TITLE: Motilin-related peptide and ghrelin: lessons from molecular techniques, peptide chemistry, and receptor biology.
COMMENT: Comment on: Gastroenterology. 2000 Aug;119(2):395-405
AUTHOR: Del Rincon J P; Thorner M O; Gaylinn B G
SOURCE: GASTROENTEROLOGY, (2001 Feb) 120 (2) 587-8; author reply 589.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20030111
Entered Medline: 20010329

L19 ANSWER 67 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 24
ACCESSION NUMBER: 2001-590033 [66] WPIDS
DOC. NO. CPI: C2001-175008
TITLE: New cyclobutene derivatives are motolin receptor antagonists useful in treatment of irritable bowel syndrome and esphageal reflux resulting from administration of erythromycin..
DERWENT CLASS: B05
INVENTOR(S): CHEN, R H; XIANG, M A
PATENT ASSIGNEE(S): (CHEN-I) CHEN R H; (XIAN-I) XIANG M A; (ORTH) ORTHO-MCNEIL PHARM INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001068622	A1	20010920	(200166)*	EN	38
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
US 2001056106	A1	20011227	(200206)		
AU 2001047357	A	20010924	(200208)		
US 6384031	B1	20020507	(200235)		
US 2002103238	A1	20020801	(200253)		
US 6667309	B2	20031223	(200408)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001068622	A1		WO 2001-US7704	20010309
US 2001056106	A1	Provisional	US 2000-188919P	20000313
			US 2001-803565	20010309
AU 2001047357	A		AU 2001-47357	20010309
US 6384031	B1	Provisional	US 2000-188919P	20000313
			US 2001-803565	20010309
US 2002103238	A1	Provisional	US 2000-188919P	20000313
		Div ex	US 2001-803565	20010309
			US 2002-95981	20020312
US 6667309	B2	Provisional	US 2000-188919P	20000313
		Div ex	US 2001-803565	20010309
			US 2002-95981	20020312

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001047357 A	Based on		WO 2001068622
US 2002103238 A1	Div ex		US 6384031
US 6667309	B2	Div ex	US 6384031

PRIORITY APPLN. INFO: US 2000-188919P 20000313; US 2001-803565 20010309; US 2002-95981 20020312

AN 2001-590033 [66] WPIDS

AB WO 200168622 A UPAB: 20011113

NOVELTY - Cyclobutene derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Cyclobutene derivatives of formula (I) and their salts are new.

R1 = H, 1-5C alkyl (optionally substituted with halo), amino 1-5C alkyl, 1-5C alkylamino 1-5C alkyl, di(1-5C)alkylamino 1-5C alkyl, 1-5C alkylcarbonyl, 1-5C alkoxycarbonyl, aminocarbonyl, 1-9C alkylaminocarbonyl, 3-9C cycloalkylaminocarbonyl, heteroarylaminocarbonyl (optionally substituted with 1 or more 1-5C alkyl), pyridinylcarbonyl (optionally substituted with 1 or more halo or 1-5C alkyl), thiophenecarbonyl (optionally substituted with 1 or more halo or 1-5C alkyl) or phenyl, phenyl 1-5C alkyl, phenoxycarbonyl, phenylcarbonyl, diphenylmethylcarbonyl, phenylaminocarbonyl, phenylthiocarbonyl or phenylaminothiocarbonyl (each optionally substituted with 1 or more halo, 1-5C alkyl, trihalomethyl, 1-5C alkoxy, NH2, CN, NO2, 1-5C alkylamino or di(1-5C)alkylamino, which may be taken together to form a fused bicyclic aromatic ring or together with the phenyl ring to form a fused bicyclic 7-10 membered heterocyclic ring having 1-2 heteroatoms selected from O, N and S) or RaRbN-(1-5C)alkyl;

Ra and Rb = H or 1-5C alkyl or together form morpholine, piperazine or piperidine (optionally N-substituted with 1-5C alkyl or phenyl 1-5C alkyl);

R2 = H, 1-5C alkyl, 1-5C alkoxy, phenyl (optionally substituted with 1 or more halo or 1-5C alkyl) or phenyl 1-5C alkyl (optionally substituted with halo, 1-5C alkyl, 1-5C alkoxy, halo or di-(1-5C)alkylamino);

R3 = H, 1-5C alkylcarbonyl (optionally substituted with halo) or phenylcarbonyl (optionally substituted with one or more halo, 1-5C alkyl, 1-5C alkoxy, NH2, 1-5C alkylamino or di(1-5C)alkylamino);

R4 = H, 1-5C alkyl, 1-5C alkylcarbonyl (optionally substituted with halo) or phenylcarbonyl (optionally substituted with 1 or more halo, 1-5C alkyl, 1-5C alkoxy, NH2, 1-5C alkylamino or di(1-5C)alkylamino;

n = 0-3;

m = 1-5;

R5 = X-(CH2)q-(A)t;

q = 0-3;

t = 0-1;

X = O, CH2, S, OH, SH or NRc;

Rc = H, 1-5C alkyl, morpholino 1-5C alkyl, piperidinyl 1-5C alkyl, N-phenylmethylpiperidinyl or piperazinyl 1-5C alkyl with the proviso that if q and t = 0, X = OH, SH or NH2;

A = 1-5C alkoxycarbonyl, phenylcarbonyl or R7R8N-;

R7 and R8 = H, 1-5C alkyl or 3-9C cycloalkyl; or

R7 + R8 = 5-6 membered heterocyclic ring with 1 or more heteroatoms selected from O, N, S and their sulfoxides and N-oxides; and

R6 = H, halo, 1-5C alkoxy, 1-5C alkylamino or di(1-5C)alkylamino.

ACTIVITY - Antiinflammatory; gastrointestinal gen.

MECHANISM OF ACTION - **Motilin receptor** antagonist.

USE - (I) are useful for treating conditions associated with **motilin receptor** activity, particularly irritable bowel syndrome or esophageal reflux as a gastrointestinal side effect resulting from administration of erythromycin.

Dwg.0/0

L19 ANSWER 68 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 25

ACCESSION NUMBER: 2001-607452 [69] WPIDS
DOC. NO. CPI: C2001-180510
TITLE: 1-Aryl(alkyl)aminomethyl cyclohexene-3-amine derivatives as non-peptidyl **motilin receptor** antagonists, use in gastrointestinal disorders, e.g., irritable bowel, esophageal reflux, and from erythromycin side effects.
DERWENT CLASS: B05
INVENTOR(S): CHEN, R H; XIANG, M A
PATENT ASSIGNEE(S): (CHEN-I) CHEN R H; (XIAN-I) XIANG M A; (ORTH) ORTHO-MCNEIL PHARM INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001068621	A1	20010920	(200169)*	EN	40
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
US 2002002192	A1	20020103	(200207)		
AU 2001050820	A	20010924	(200208)		
US 6423714	B1	20020723	(200254)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001068621	A1	WO 2001-US7701	20010309
US 2002002192	A1 Provisional	US 2000-188732P	20000313
		US 2001-803572	20010309
AU 2001050820	A	AU 2001-50820	20010309
US 6423714	B1 Provisional	US 2000-188732P	20000313
		US 2001-803572	20010309

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001050820	A Based on	WO 2001068621

PRIORITY APPLN. INFO: US 2000-188732P 20000313; US 2001-803572 20010309

AN 2001-607452 [69] WPIDS

AB WO 200168621 A UPAB: 20011126

NOVELTY - New 1-Aryl(alkyl)aminomethyl cyclohexene-3-amine derivatives (I).

DETAILED DESCRIPTION - 1-Aryl(alkyl)aminomethyl cyclohexene-3-amine derivatives of formula (I) and their salts are new:

R1 = 1-5C alkyl (optionally substituted by halogen, amino, or mono- or di- (1-5C alkyl)amino), 2-6C alkylcarbonyl or alkoxycarbonyl, aminocarbonyl. mono- or di- (1-5C alkyl)aminocarbonyl, heteroarylaminocarbonyl (optionally substituted by 1-5C alkyl), pyridylcarbonyl or thiophencarbonyl (both optionally substituted by halogen or 1-5C alkyl), or phenyl, phenyl 1-5C alkyl, benzoyl, phenoxycarbonyl, diphenylmethylcarbonyl, phenylaminocarbonyl, phenylthiocarbonyl, or phenylaminothiocarbonyl (all optionally substituted by W');

W' = halogen, 1-5C alkyl or alkoxy, trihalomethyl, amino, cyano, nitro, mono- or di- (1-5C alkyl)amino, Ra'Rb'N(1-5C alkyl); or

two W' together complete = a fused bicyclic carbocyclic or 7-10 membered heterocyclic ring containing 1-2 atoms from N, O, S;
Ra', Rb' = H or 1-5C alkyl; or
NRa'Rb' together = morpholinyl, piperazinyl, or piperidinyl (optionally substituted by 1-5C alkyl or phenyl 1-5C alkyl);
R2 = H, 1-5C alkyl or alkoxy, phenyl (optionally substituted by halogen or 1-5C alkyl), or phenyl 1-5C alkyl (optionally substituted by halogen, 1-5C alkyl or alkoxy, or di-(1-5C alkyl)amino);
R3 = H, 2-6C alkylcarbonyl, or benzoyl (optionally substituted by halogen, 1-5C alkyl or alkoxy, amino, or mono- or di- (1-5C alkyl)amino);
R4 = 1-5C alkyl, or as for R3;
n = 0-3;
m = 1-5;
R5 = X-(CH2)q-(A)t;
q = 0-3;
t = 0 or 1;
X = O, CH2, S, hydroxy, thiol, or NRc';
Rc' = H, or 1-5C alkyl (optionally substituted by morpholinyl, piperidinyl, phenylmethyl, or piperazinyl);
A = 2-6C alkoxycarbonyl, benzoyl, or NR7R8;
R7, R8 = H, 1-5C alkyl, or 1-9C cycloalkyl; or
NR7R8 together = 5-6 membered heterocyclyl containing heteroatoms from O, N, S or their N-oxides or sulfoxides; and
R6 = H, halogen, 1-5C alkoxy, or mono- or di- (1-5C alkyl)amino.
With the proviso that, when q and t = 0, then X = hydroxy, thiol, or amino.
ACTIVITY - Gastrointestinal; antiinflammatory.
MECHANISM OF ACTION - (I) are antagonists of the **motilin receptor**, responsible for increased gastrointestinal activity. A protocol is written for testing the compounds for inhibition of motilin and erythromycin induced contractions in rabbit duodenal smooth muscle, but no results are given.
USE - (I) are of use in gastrointestinal motility disorders, including irritable bowel syndrome and esophageal reflux. These may be caused as gastrointestinal side effects of erythromycin administration.
Dwg.0/0

L19 ANSWER 69 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 26

ACCESSION NUMBER: 2001-602736 [68] WPIDS
DOC. NO. CPI: C2001-178569
TITLE: Cyclopentane derivatives useful for treating conditions associated with **motilin receptor** activity such as irritable bowel syndrome or esophageal reflux.
DERWENT CLASS: B05
INVENTOR(S): CHEN, R H; XIANG, M A
PATENT ASSIGNEE(S): (CHEN-I) CHEN R H; (XIAN-I) XIANG M A; (ORTH) ORTHO-MCNEIL PHARM INC
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001068620	A1	20010920	(200168)*	EN	26
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
US 2001041701	A1	20011115	(200172)		
AU 2001049144	A	20010924	(200208)		
US 6392040	B1	20020521	(200239)		
US 2002111484	A1	20020815	(200256)		

US 6624165 B2 20030923 (200364)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001068620	A1		WO 2001-US7703	20010309
US 2001041701	A1	Provisional	US 2000-188917P	20000313
			US 2001-803605	20010309
AU 2001049144	A		AU 2001-49144	20010309
US 6392040	B1	Provisional	US 2000-188917P	20000313
			US 2001-803605	20010309
US 2002111484	A1	Provisional	US 2000-188917P	20000313
		Div ex	US 2001-803605	20010309
			US 2002-119255	20020409
US 6624165	B2	Provisional	US 2000-188917P	20000313
		Div ex	US 2001-803605	20010309
			US 2002-119255	20020409

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001049144	A	Based on	WO 2001068620
US 2002111484	A1	Div ex	US 6392040
US 6624165	B2	Div ex	US 6392040

PRIORITY APPLN. INFO: US 2000-188917P 20000313; US 2001-803605 20010309; US 2002-119255 20020409

AN 2001-602736 [68] WPIDS

AB WO 200168620 A UPAB: 20011121

NOVELTY - Cyclopentane derivatives (I) or their salts, are new.

DETAILED DESCRIPTION - Cyclopentane derivatives of formula (I) or their salts, are new:

R1 = heteroarylaminocarbonyl (optionally substituted with 1 or more 1-5C alkyl);

R2 = H, 1-5C alkyl, 1-5C alkoxy, phenyl (optionally substituted by 1 or more halogen), 1-5C alkyl, phenyl 1-5C alkyl (optionally substituted with 1 or more halogen), 1-5C alkyl, 1-5C alkoxy, halo or di-1-5C alkylamino;

R3 = H, 1-5C alkylcarbonyl (optionally substituted with halogen), phenylcarbonyl (optionally substituted with 1 or more from halogen, 1-5C alkyl, 1-5C alkoxy, NH2, 1-5C alkylamino or di-1-5C alkylamino;

R4 = H, 1-5C alkyl, 1-5C alkylcarbonyl (optionally substituted with halogen), phenylcarbonyl (optionally substituted with 1 or more from halogen, 1-5C alkyl, 1-5C alkoxy, NH2, 1-5C alkylamino or di-1-5C alkylamino);

n = 0-3;

m = 1-5;

R5 = X-(CH2)q-(A)t;

q = 0-3;

t = 0-1;

X = O, CH2, S, OH, SH, NRc;

R6 = H, halogen, 1-5C alkoxy, 1-5C alkylamino and di-1-5C alkylamino;

Rc = H, 1-5C alkyl, morpholino-1-5C alkyl, piperidinyl-1-5C alkyl, N-phenylmethylpiperidinyl, piperazinyl-1-5C alkyl; with the proviso that if q and t = 0;

X = OH, SH or NH2;

A = 1-5C alkoxycarbonyl, phenylcarbonyl or R7R8N; where

R7, R8 = H, 1-5C alkyl, cyclo 1-9C alkyl; and

R7+ R8 form a 5-6 membered heterocyclic ring with 1 or more heteroatoms selected from O, N, S, their sulfoxides, N-oxides or salts.

INDEPENDENT CLAIMS are also included for:

(1) a method for treating a condition associated with **motilin receptor** activity comprising administering (I); and

(2) a method for treating gastrointestinal side effects resulting from administration of erythromycin comprising administering (I).

ACTIVITY - Antiinflammatory.

MECHANISM OF ACTION - **Motilin receptor** antagonists. 3-Benzyl-3-trichloroacetylamino-N-((3-(2-morpholinoethoxy)phenyl)-N-((1,3,4-thiadiazol-2-yl)aminocarbonyl)amino)methylcyclopentene was evaluated for its ability to compete with radiolabeled motilin (porcine) for the **motilin receptors** located on the colon of mature rabbits and was found to exhibit 17% inhibition at 100 nM.

USE - For treating a condition associated with **motilin receptor** activity, preferably irritable bowel syndrome or esophageal reflux (claimed) and gastrointestinal side effects of erythromycin.

ADVANTAGE - The compounds are non-peptidyl and display efficacy and potency comparable to know motilin and erythromycin antagonists.

Dwg.0/0

L19 ANSWER 70 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 27

ACCESSION NUMBER: 2001-343479 [36] WPIDS
DOC. NO. NON-CPI: N2001-248744
DOC. NO. CPI: C2001-106338
TITLE: Novel polypeptides related to dog and rabbit **motilin receptor** polypeptide, comprising unique regions from dog and **motilin receptor** amino acid sequence, useful for identifying compounds for treating diarrhea in humans.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): MCKEE, K; TAN, C
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001032710	A1	20010510	(200136)*	EN	41
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
EP 1228096	A1	20020807	(200259)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2003512859	W	20030408	(200333)		50

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001032710	A1	WO 2000-US29426	20001025
EP 1228096	A1	EP 2000-975380	20001025
		WO 2000-US29426	20001025
JP 2003512859	W	WO 2000-US29426	20001025
		JP 2001-535408	20001025

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1228096	A1	Based on	WO 2001032710
JP 2003512859	W	Based on	WO 2001032710

PRIORITY APPLN. INFO: US 1999-162264P 19991029
AN 2001-343479 [36] WPIDS
AB WO 200132710 A UPAB: 20010628
NOVELTY - A purified polypeptide (I) comprising unique region (UR) of fully defined dog **motilin receptor** (MR) exon 1

sequence of 271 amino acids (aa) (S1) or rabbit MR sequence of 400 aa (S2) that is at least 9 contiguous aa in length, is new. UR is not present in fully defined human MR sequence of 412 aa (S5) or Spheroides nephelus 75E7 sequence of 363 aa (S6). All sequences are given in specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a purified nucleic acid (II) comprising a nucleotide sequence encoding (I) and which comprises unique nucleotide sequence of a fully defined dog MR exon I polynucleotide sequence of 813 nucleotides (S3) or rabbit MR polynucleotide sequence of 1203 nucleotides (S4), that is 18 contiguous nucleotides in length or the complement of (II). The UR of (II) is not present in a fully defined human MR polynucleotide sequence of 1239 nucleotides (S7) or S.nephelus polynucleotide sequence of 1092 nucleotides (S8). All sequences are given in specification;

(2) an expression vector (III) comprising a recombinant nucleotide sequence encoding for a unique amino acid region of (S1) or (S2) that is at least 9 contiguous amino acids in length, where the unique region is not present in (S5) or (S6);

(3) a recombinant cell (IV) comprising (III) functionally coupled to a promoter recognized by the cell; and

(4) a recombinant cell made by a process which involves introducing (III).

ACTIVITY - Antidiarrheic; antiinflammatory.

No supporting data is given.

MECHANISM OF ACTION - **Motilin receptor** activity modulator.

USE - (IV) which comprises a recombinant nucleic acid expressing functional MR that comprises unique amino acid region of (S1) or (S2) as described above is useful for measuring the ability of a compound to affect MR activity which involves contacting (IV) with the compound and measuring MR activity. (IV) is also useful for preparing MR polypeptide by recombinant techniques (claimed). (I) and (II) are useful in a in vitro functional assay that measures whether a compound acts differentially on dog or rabbit MR than at human MR. This assay thus helps to evaluate whether a dog or rabbit model provides a useful test system in looking for a human therapeutic compound which is useful for treating gastrointestinal diseases and disorders such as gastric motility disorders, gastroparesis, irritable bowel syndrome, and diarrhea. The compounds can also be used as research tool for studying MR activity. (I) can be used as an immunogen to produce antibodies binding to dog or rabbit MR and as a target. (II) can be used to obtain nucleic acid sequences encoding full length dog MR to obtain nucleic acid encoding for MR from additional sources and to artificially produce a MR.

Dwg.0/2

L19 ANSWER 71 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:380558 BIOSIS

DOCUMENT NUMBER: PREV200100380558

TITLE: Phenethylamine derivatives.

AUTHOR(S): Kotake, Ken-ichiro [Inventor, Reprint author]; Kozono, Toshiro [Inventor]; Sato, Tsutomu [Inventor]; Takanashi, Hisanori [Inventor]

CORPORATE SOURCE: Shizuoka, Japan
ASSIGNEE: Chugai Seiyaku Kabushiki Kaisha, Tokyo, Japan

PATENT INFORMATION: US 6255285 July 03, 2001

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 3, 2001) Vol. 1248, No. 1. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.

DOCUMENT TYPE: Patent

LANGUAGE: English

ENTRY DATE: Entered STN: 8 Aug 2001
Last Updated on STN: 19 Feb 2002

AB The present invention has as its object providing phenethylamine derivatives that typically function as a **motilin receptor** antagonist and which are useful as medicines. The

invention provides compounds represented by the general formula (1): ##STR1## (wherein A is typically an amino acid residue, R1 is typically R6 --CO--, R2 is typically a hydrogen atom, R3 is typically --CO--R7, R4 is typically an alkyl group, R5 is typically a hydroxyl group, R6 is typically an alkyl group, and R7 is typically an amino group).

L19 ANSWER 72 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-082889 [11] WPIDS
DOC. NO. CPI: C2002-025062
TITLE: New substituted diamine derivatives, useful as motilin antagonists for treating gastrointestinal reflux, eating disorders leading to obesity and irritable bowel disorder.
DERWENT CLASS: B05
INVENTOR(S): JOHNSON, S G; RIVERO, R A
PATENT ASSIGNEE(S): (JOHN-I) JOHNSON S G; (RIVE-I) RIVERO R A; (ORTH) ORTHO-MCNEIL PHARM INC
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001085694	A2	20011115	(200211)*	EN	131
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
US 2002013352	A1	20020131	(200216)		
AU 2001053374	A	20011120	(200219)		
US 6511980	B2	20030128	(200311)		
EP 1294695	A2	20030326	(200323)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2003203906	A1	20031030	(200372)		
CZ 2002003646	A3	20031015	(200374)		
JP 2003532710	W	20031105	(200377)		152
CN 1440390	A	20030903	(200380)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001085694	A2		WO 2001-US11821	20010411
US 2002013352	A1	Provisional	US 2000-202131P	20000505
			US 2001-829767	20010410
AU 2001053374	A		AU 2001-53374	20010411
US 6511980	B2	Provisional	US 2000-202131P	20000505
			US 2001-829767	20010410
EP 1294695	A2		EP 2001-926866	20010411
			WO 2001-US11821	20010411
US 2003203906	A1	Provisional	US 2000-202131P	20000505
		Div ex	US 2001-829767	20010410
			US 2002-291133	20021108
CZ 2002003646	A3		WO 2001-US11821	20010411
			CZ 2002-3646	20010411
JP 2003532710	W		JP 2001-582295	20010411
			WO 2001-US11821	20010411
CN 1440390	A		CN 2001-812050	20010411

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2001053374 A Based on WO 2001085694
EP 1294695 A2 Based on WO 2001085694
US 2003203906 A1 Div ex US 6511980
CZ 2002003646 A3 Based on WO 2001085694
JP 2003532710 W Based on WO 2001085694

PRIORITY APPLN. INFO: US 2000-202131P 20000505; US 2001-829767 20010410; US 2002-291133 20021108

AN 2002-082889 [11] WPIDS

AB WO 200185694 A UPAB: 20020215

NOVELTY - Substituted diamine derivatives (I) and their salts, esters and prodrugs are new.

DETAILED DESCRIPTION - Substituted diamine derivatives of formula (I) and their salts, esters and prodrugs are new.

R1 = H, aryl, aralkyl, heterocyclyl, diarylalkyl, heterocyclyl-alkyl or lower alkyl, where alkyl, aryl and heterocyclyl moieties are optionally substituted by one or more halo, hydroxy, nitro, carboxy, cyano, amino, dialkylamino, lower alkoxy, lower alkyl, trihalomethyl, alkylamino, carboxy or alkoxycarbonyl;

R2 = aryl, aralkyl, cycloalkyl, cycloalkyl-alkyl heterocyclyl, heterocyclyl-alkyl, diarylalkyl, aminoalkyl, trihalomethyl, arylamino or lower alkyl, where the alkyl, aryl, heterocyclyl-alkyl, heterocyclyl or amino moieties are optionally substituted by one or more halo, hydroxy, nitro, cyano, amino, dialkylamino, lower alkoxy, lower alkyl, tri-halomethyl, alkylamino, phenyl, carboxy, carboxyalkyl or alkoxycarbonyl;

X1-X4 = absent, CO or SO2;

provided that at least one of X1 or X2 and at least one of X3 or X4 is CO and SO2; or

R1, R2 and X1 can be taken together (with the amine nitrogen) to form a monocyclic or fused bicyclic or tricyclic secondary amine ring structure, where the monocyclic or fused bicyclic or tricyclic secondary amine ring structure is optionally substituted by one or more halo, oxo, nitro, cyano, amino, alkylamino, dialkylamino, trialkylamino, lower alkoxy, lower alkyl, tri-halomethyl, carboxy, acetyloxy, alkoxycarbonyl, aryl, aralkyl or heterocyclyl;

A = lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-alkyl, alkyl-cycloalkyl, cycloalkenyl, cycloalkenyl-alkyl, alkyl-cycloalkenyl, alkyl-cycloalkyl-alkyl, alkyl-aryl-alkyl, alkyl-aryl, aryl-alkyl or phenyl; where, in each case, the A group is optionally substituted by one or more R7;

R7 = alkyl, tri-halomethyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclyl-alkyl, diarylalkyl, aminoalkyl, or arylamino; where the alkyl, aryl, heterocyclyl-alkyl, heterocyclyl, or amino moieties are optionally substituted by one or more halogen, hydroxy, nitro, cyano, amino, dialkylamino, lower alkoxy, lower alkyl, tri-halomethyl, alkylamino, phenyl, carboxy or alkoxycarbonyl;

provided that A is not -1,3-cyclopentyl-1-ene-alkyl;

R3 = H, aryl, heterocyclyl, aralkyl, diarylalkyl, heterocyclo-alkyl, tri-halomethyl, alkylamino, arylamino or lower alkyl, where the aryl, heterocyclyl, aralkyl, diarylalkyl, heterocyclyl-alkyl, alkylamino, arylamino or lower alkyl may be substituted by one or more halogen, nitro, cyano, amino, dialkylamino, lower alkoxy, lower alkyl, tri-halomethyl, carboxy or alkoxycarbonyl;

Y = O, NH, S or SO2;

n = 0-5;

R4 = H, amino, alkylamino, dialkylamino, N-alkyl-N-aralkyl-amino, trialkylamino, dialkylaminoalkoxyalkyl, heterocyclyl, heterocyclyl-alkyl, oxo-substituted heterocyclyl or lower alkyl substituted heterocyclyl;

R5 = H, halo, nitro, cyano, amino, alkylamino, dialkylamino, trialkylamino, lower alkoxy, lower alkyl, trihalomethyl, carboxy or alkoxycarbonyl.

An INDEPENDENT CLAIM is also included for intermediates of formula (XXX) and their salts, esters and prodrugs:

X4' = CO or SO2;

A1 = as for A.
ACTIVITY - Antiinflammatory; anorectic.
MECHANISM OF ACTION - **Motilin receptor** antagonist.
In an in vitro **motilin receptor** binding assay using rabbit colon, N-(3-(2-(1-pyrrolidino)ethyloxy)phenyl)-N-(cis-3-(benzylamino)cyclohexyl)methyl-4-fluorophenylcarboxamide (Ia) exhibited an IC50 value of 0.029 micro M corresponding to 95% inhibition.
USE - For treating a **motilin receptor** associated condition or disorder, e.g. gastrointestinal reflux, eating disorders leading to obesity and irritable bowel disorder (all claimed).
ADVANTAGE - (I) are non-peptidyl motilin antagonists and compete with motilin and erythromycin for the **motilin receptor** site with potencies and activities comparable to known peptidyl motilin antagonists such as OHM 11526. Unlike peptidyl antagonists, (I) are suitable for oral administration since (I) are not susceptible to the enzymes of the digestive tract.
Dwg.0/0

L19 ANSWER 73 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-451586 [48] WPIDS
DOC. NO. CPI: C2001-136345
TITLE: Combinations, used to treat altered gastrointestinal motility, sensitivity, secretion and/or abdominal disorders, comprise serotonin-4 receptor partial agonist and co-agent e.g. proton pump inhibitor.
DERWENT CLASS: B02
INVENTOR(S): BILLSTEIN, S A; DUMOVIC, P; FRANCO, N; IWICKI, M T; PFANNKUCHE, H; WILUSZ, E J
PATENT ASSIGNEE(S): (NOVS) NOVARTIS AG; (NOVS) NOVARTIS PHARMA GMBH; (NOVS) NOVARTIS-ERFINDUNGEN VERW GMBH
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001041748	A2	20010614	(200148)*	EN	30
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001026728	A	20010618	(200161)		
CZ 2002001967	A3	20020814	(200263)		
BR 2000016275	A	20020827	(200265)		
NO 2002002680	A	20020812	(200265)		
EP 1286668	A2	20030305	(200319)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
SK 2002000806	A3	20030401	(200331)		
KR 2003016208	A	20030226	(200341)		
CN 1409634	A	20030409	(200345)		
JP 2003523324	W	20030805	(200353)		46
HU 2003001122	A2	20030828	(200363)		
MX 2002005695	A1	20020901	(200370)		
ZA 2002004493	A	20031126	(200402)		47

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001041748	A2	WO 2000-EP12420	20001208
AU 2001026728	A	AU 2001-26728	20001208
CZ 2002001967	A3	WO 2000-EP12420	20001208

		CZ 2002-1967	20001208
BR 2000016275	A	BR 2000-16275	20001208
		WO 2000-EP12420	20001208
NO 2002002680	A	WO 2000-EP12420	20001208
		NO 2002-2680	20020606
EP 1286668	A2	EP 2000-989967	20001208
		WO 2000-EP12420	20001208
SK 2002000806	A3	WO 2000-EP12420	20001208
		SK 2002-806	20001208
KR 2003016208	A	KR 2002-707332	20020608
CN 1409634	A	CN 2000-816881	20001208
JP 2003523324	W	WO 2000-EP12420	20001208
		JP 2001-543093	20001208
HU 2003001122	A2	WO 2000-EP12420	20001208
		HU 2003-1122	20001208
MX 2002005695	A1	WO 2000-EP12420	20001208
		MX 2002-5695	20020607
ZA 2002004493	A	ZA 2002-4493	20020605

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001026728	A	Based on	WO 2001041748
CZ 2002001967	A3	Based on	WO 2001041748
BR 2000016275	A	Based on	WO 2001041748
EP 1286668	A2	Based on	WO 2001041748
SK 2002000806	A3	Based on	WO 2001041748
JP 2003523324	W	Based on	WO 2001041748
HU 2003001122	A2	Based on	WO 2001041748
MX 2002005695	A1	Based on	WO 2001041748

PRIORITY APPLN. INFO: US 1999-458388 19991210
AN 2001-451586 [48] WPIDS
AB WO 200141748 A UPAB: 20010829
NOVELTY - Pharmaceutical combinations comprising a 1st agent that is a serotonin (5-HT4) receptor partial agonist or its pharmaceutically acceptable salts, racemates or enantiomers and a co-agent or its pharmaceutically acceptable salts, racemates or enantiomers.

ACTIVITY - Tranquilizer; antidepressant; antiinflammatory; relaxant; antiemetic; antiulcer; laxative; antidiarrheic.

In a double-blind, placebo-controlled study, after 1 week of screening and a 2-week drug-free baseline period twice daily, patients with heartburn were randomized to orally receive placebo, tegaserod 0.4, 1 or 4 mg/day, ranitidine 300 mg/day, omeprazole 20 mg/day, tegaserod 0.4, 1 or 4 mg/day plus ranitidine 300 mg/day or tegaserod 0.4, 1 or 4 mg/day plus omeprazole 20 mg/day twice daily for 8 weeks. Each administration was 30 minutes before meals in the morning and evening. Only Maalox (RTM: aluminum hydroxide) tablets could be used for rescue medication. The combinations of tegaserod with omeprazole and tegaserod with ranitidine significantly reduced the episodes of heartburn occurring per week in the 8-week period of the double-blind, placebo-controlled period of the study compared with placebo, tegaserod, ranitidine or omeprazole alone. The combinations also reduced other symptoms of gastro-esophageal reflux disease (GERD) including abdominal pain, bloating and regurgitation. Patients showed a significant improvement in quality of life factors compared to placebo or any of the agents alone.

MECHANISM OF ACTION - 5-HT3 receptor antagonist; 5-HT4 receptor antagonist, 5-HT4 receptor agonist; histamine H2 receptor antagonist; proton pump inhibitors; selective serotonin reuptake inhibitor; muscarinic1 receptor agonist; muscarinic1 antagonist; cholecystokinin receptor antagonist; opioid receptor agonist; opioid receptor antagonist; **motilin receptor** antagonist; **motilin receptor** agonists; nitric oxide synthase inhibitor; gamma -amino butyric acid (GABA)B receptor agonist; GABAB receptor modulator;

neurokinin receptor antagonist; neurokinin receptor agonist; calcitonin gene-related peptide receptor antagonist; calcitonin gene-related peptide receptor agonist; corticotrophin releasing factor receptor antagonist; corticotrophin releasing factor receptor agonist; mast cell stabilizer; dopamine D2 antagonist; somatostatin receptor antagonists.

USE - The compositions are used to treated altered gastrointestinal motility, sensitivity and/or secretion and/or abdominal disorders (claimed) including heartburn, bloating, postoperative ileus, abdominal pain and discomfort, early satiety, epigastric pain, nausea, vomiting, burbulence (sic), regurgitation, intestinal pseudoobstruction, anal incontinence, gastro-esophageal reflux disease (GERD), irritable bowel syndrome, dyspepsia, chronic constipation or diarrhea, gastroparesis e.g. diabetic gastroparesis, ulcerative colitis, Crohn's disease and ulcers and their associated visceral pain. They may also be used as laxatives, as to prepare patients for colonoscopy or as a means of regulating, stabilizing or normalizing gastrointestinal disorders though regulation, stabilization or normalization of enterochromaffin cell functions, gastrointestinal secretion, afferent and efferent fiber activity. They may also be used to treat menstrual cramps or spastic or interstitial cystitis.

ADVANTAGE - The compositions produce enhanced treatment responses for altered gastrointestinal motility, sensitivity and/or secretion and/or abdominal disorders and enhanced reduction of gastrointestinal pain and other symptoms normally associated with disturbed/altered gastrointestinal motility, sensitivity and/or secretion and/or abdominal disorders.

Dwg.0/0

L19 ANSWER 74 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:396891 CAPLUS
DOCUMENT NUMBER: 135:14332
TITLE: Method of forming a peptide-receptor complex with protein zsig33 and growth hormone secretagogue receptor (GHS-R)
INVENTOR(S): Sheppard, Paul O.; Jaspers, Stephen R.; Deisher, Theresa A.; Bishop, Paul D.
PATENT ASSIGNEE(S): Zymogenetics, Inc., USA
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001038355	A2	20010531	WO 2000-US32074	20001122
WO 2001038355	A3	20011122		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1232175	A2	20020821	EP 2000-982197	20001122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003514917	T2	20030422	JP 2001-540118	20001122

PRIORITY APPLN. INFO.: US 1999-166765P P 19991122
WO 2000-US32074 W 20001122

AB The present invention relates to a method of forming a peptide-receptor complex with zsig33 polypeptides and growth hormone secretagogue receptor (GHS-R). The discovery of this novel method of forming a peptide-receptor complex is important for further elucidation of the how the body maintains

its nutritional homeostasis and development of therapeutics to intervene in those processes, as well as other uses that will be apparent from the teachings herein. The present invention is based upon the identification of a previously described secreted protein known as zsig33 as the peptide ligand for an orphan receptor known as GHS-R, which belongs to G protein-coupled receptor family. The zsig33 ligand has homol. to motilin and has been found to be transcribed in the gastrointestinal system. The orphan receptor has homol. to the **motilin receptor**, GPR38. Anal. of the tissue distribution of the mRNA corresponding to zsig33 protein showed that expression was highest in stomach, followed by apparent but decreased expression levels in small intestine and pancreas. The partial sequence for the secreted zsig33 protein was derived from a pancreatic library, and has also been shown in lung cDNA libraries. In vitro binding studies have shown that the zsig33 peptide binds to kidney, duodenum, and jejunum. Thus, binding of the zsig33 ligand to the GHS-R is expected in tissues such as stomach, small intestine, pancreas, lung, kidney, duodenum, jejunum, and brain. Methods of modulating gastric contractility, nutrient uptake, growth hormones, the secretion of digestive enzymes and hormones, and/or secretion of enzymes and/or hormones in the pancreas are also included.

L19 ANSWER 75 OF 391 MEDLINE on STN DUPLICATE 28
ACCESSION NUMBER: 2001527205 MEDLINE
DOCUMENT NUMBER: 21443751 PubMed ID: 11461914
TITLE: Identification of peptide ligand-binding domains within the human **motilin receptor** using photoaffinity labeling.
AUTHOR: Coulie B; Matsuura B; Dong M; Hadac E M; Pinon D I; Feighner S D; Howard A D; Miller L J
CORPORATE SOURCE: Center for Basic Research in Digestive Diseases, Departments of Internal Medicine and Biochemistry/Molecular Biology, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Sep 21) 276 (38) 35518-22.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20030105
Entered Medline: 20011025

AB The cDNA encoding the human **motilin receptor** was recently cloned and found to represent a G protein-coupled receptor that is structurally related to the growth hormone secretagogue receptors. Together, these represent a new Class I receptor family. Our aim in the present work is to gain insight into the molecular basis of binding of motilin to its receptor using photoaffinity labeling. To achieve this, we developed a Chinese hamster ovary cell line that overexpressed functional **motilin receptor** (CHO-MtlR; 175,000 sites per cell, with K(i) = 2.3 +/- 0.4 nm motilin and EC(50) = 0.3 +/- 0.1 nm motilin) and a radioiodinatable peptide analogue of human motilin that incorporated a photolabile p-benzoyl-l-phenylalanine (Bpa) residue into its pharmacophoric domain. This probe, [Bpa(1),Ile(13)]motilin, was a full agonist at the **motilin receptor** that increased intracellular calcium in a concentration-dependent manner (EC(50) = 1.5 +/- 0.4 nm). This photolabile ligand bound specifically and with high affinity to the **motilin receptor** (K(i) = 12.4 +/- 1.0 nm), and covalently labeled that molecule within its M(r) = 45,000 deglycosylated core. Cyanogen bromide cleavage demonstrated its covalent attachment to fragments of the receptor having apparent M(r) = 6,000 and M(r) = 31,000. These were demonstrated to represent fragments that included both the first and the large second extracellular loop domains,

with the latter representing a unique structural feature of this receptor. The spatial approximation of the pharmacophoric domain of motilin with these receptor domains support their functional importance as well.

L19 ANSWER 76 OF 391 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 2002176648 MEDLINE
DOCUMENT NUMBER: 21905352 PubMed ID: 11908678
TITLE: Fourteen-membered ring macrolides as anti-angiogenic compounds.
AUTHOR: Yatsunami J; Hayashi S
CORPORATE SOURCE: The Department of Internal Medicine, Saga Medical School, Nabeshima, Japan.. yatsunam@post.saga-med.ac.jp
SOURCE: ANTICANCER RESEARCH, (2001 Nov-Dec) 21 (6B) 4253-8. Ref: 82
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020324
Last Updated on STN: 20020405
Entered Medline: 20020404

AB Macrolide antibiotics have been widely used for infectious diseases since the 1950s. For the last decade, 14-membered ring macrolides, of which erythromycin is the prototype, have attracted a great deal of attention because of their additional therapeutical activities far beyond antibiotics. First, erythromycin has prokinetic effects on the gastrointestinal tract as a **motilin receptor** agonist. Second, 14-membered ring macrolides, including erythromycin, roxithromycin and clarithromycin have immunomodulating or anti-inflammatory effects in a variety of settings, whereas 16-membered ring macrolides do not. Recently, we found roxithromycin and clarithromycin suppressed angiogenesis and tumor growth in vivo. Both these drugs are administered per os with insignificant side-effects. Their safety has been established through the experience of long-term treatment for chronic lower respiratory infectious diseases such as diffuse panbronchiolitis. Although the precise mechanisms have not yet been clarified, 14-membered ring macrolides and their derivatives are promising in therapeutic applications for solid tumors.

L19 ANSWER 77 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 30
ACCESSION NUMBER: 2002:162363 BIOSIS
DOCUMENT NUMBER: PREV200200162363
TITLE: Human TE671 cells express functional **motilin receptors.**
AUTHOR(S): Zhou, Lubing [Reprint author]; Gunnet, Joseph W.; Moore, Mike; Cryan, Ellen V.; Xu, Jun Z.; Demarest, Keith T.
CORPORATE SOURCE: Endocrine Therapeutics, Drug Discovery, The R.W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan, NJ, 08869, USA
lzhou@prius.jnj.com
SOURCE: Biotechnology Letters, (December, 2001) Vol. 23, No. 24, pp. 2067-2073. print.
CODEN: BILED3. ISSN: 0141-5492.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

AB In our search for a cell line expressing endogenous human **motilin receptor**, we have discovered that the TE671 cell line, a neuron-derived medulloblastoma human line, expresses functional

motilin receptors. The cDNA of the receptor was isolated from the cells and its sequence was confirmed to be identical to the previously reported cDNA sequence isolated from human thyroid. The function of the receptor protein was evaluated both for its ability to inhibit the binding of 125I-motilin to a crude membrane preparation of TE671 cells and for activation of the phospholipase C signal transduction pathway by calcium mobilization assay. The precise numbers of **motilin receptor** RNA molecule in TE671 cell and 24 human tissues were quantitatively determined by real-time PCR. TE671 cell line should be a useful tool for the study of **motilin receptor**-involved signal transduction in humans.

L19 ANSWER 78 OF 391 MEDLINE on STN DUPLICATE 31
ACCESSION NUMBER: 2001636276 MEDLINE
DOCUMENT NUMBER: 21540317 PubMed ID: 11683685
TITLE: Review article: the pharmacological treatment of acute colonic pseudo-obstruction.
AUTHOR: De Giorgio R; Barbara G; Stanghellini V; Tonini M; Vasina V; Cola B; Corinaldesi R; Biagi G; De Ponti F
CORPORATE SOURCE: Department of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy.
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (2001 Nov) 15 (11) 1717-27. Ref: 93
Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011105
Last Updated on STN: 20020123
Entered Medline: 20011219

AB Acute colonic pseudo-obstruction (Ogilvie's syndrome) can be defined as a clinical condition with symptoms, signs and radiological appearance of acute large bowel obstruction unrelated to any mechanical cause. Recent reports of the efficacy of cholinesterase inhibitors in relieving acute colonic pseudo-obstruction have fuelled interest in the pharmacological treatment of this condition. The aim of the present review is to outline current perspectives in the pharmacological treatment of patients with acute colonic pseudo-obstruction. The best documented pharmacological treatment of Ogilvie's syndrome is intravenous neostigmine (2-2.5 mg), which leads to quick decompression in a significant proportion of patients after a single infusion. However, the search for new colokinetic agents for the treatment of lower gut motor disorders has made available a number of drugs that may also be therapeutic options for Ogilvie's syndrome. Among these agents, the potential of 5-hydroxytryptamine-4 receptor agonists and **motilin receptor** agonists is discussed.

L19 ANSWER 79 OF 391 MEDLINE on STN DUPLICATE 32
ACCESSION NUMBER: 2001527646 MEDLINE
DOCUMENT NUMBER: 21457500 PubMed ID: 11573597
TITLE: Gastric residual volume in children: a study comparing efficiency of erythromycin and metoclopramide as prokinetic agents.
AUTHOR: Zatman T F; Hall J E; Harmer M
CORPORATE SOURCE: Department of Anaesthesia and Intensive Care Medicine, University of Wales College of Medicine, Cardiff, UK.
SOURCE: BRITISH JOURNAL OF ANAESTHESIA, (2001 Jun) 86 (6) 869-71.
Journal code: 0372541. ISSN: 0007-0912.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011015
Entered Medline: 20011011

AB Metoclopramide may be used to stimulate gastric emptying when anaesthetizing children for emergency operations. Unfortunately, metoclopramide is associated with extrapyramidal side effects. Erythromycin, a **motilin receptor** agonist, is a prokinetic agent but its use has been little investigated in children. This randomized double-blind study compared the effects of premedication with oral metoclopramide 0.15 mg kg(-1) or erythromycin 1 mg kg(-1) on gastric emptying in 80 children undergoing tonsillectomy. Pre-operative fluids, premedication and anaesthetic technique were standardized and gastric volume was measured with an orogastric tube. Post-operative nausea and vomiting was recorded. Metoclopramide and erythromycin produced similar gastric volumes (0.29 and 0.24 ml kg(-1)) and there was no difference in post-operative vomiting. In the erythromycin group there were more patients with negative aspirates (45.9%) than in the metoclopramide group (35.1%), but the difference was not statistically significant. These results indicate that erythromycin may be as effective as metoclopramide as a prokinetic agent.

L19 ANSWER 80 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:692530 CAPLUS
DOCUMENT NUMBER: 138:354224
TITLE: Design and synthesis of novel pure motilin antagonists
AUTHOR(S): Haramura, Masayuki; Okamachi, Akira; Tsuzuki, Kouichi; Yogo, Kenji; Ikuta, Makoto; Kozono, Toshiro; Takanashi, Hisanori; Murayama, Eigoro
CORPORATE SOURCE: Chugai Biopharmaceuticals, Inc., San Diego, CA, 92121, USA
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 662-663. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A symposium report. Cyclic peptides H-Phe-cyclo[-Nε-Lys-Tyr-βAla-] and corresponding alkylated tyrosine derivs. were prepared as potent motilin antagonists. The cyclic peptides were tested for binding to the **motilin receptor** and for gastrointestinal smooth muscle contractile activity. All peptides showed binding affinity, but those with an alkyl-substituted Tyr residue were more effective. The antagonistic activity of these compds. in the contractile assay correlated with their binding activity, and no contractile activity was observed even at high concentration (> 100 μM). Substitution of Tyr with 3-tert-Bu Tyr considerably increased potency.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 81 OF 391 MEDLINE on STN DUPLICATE 33
ACCESSION NUMBER: 2001518972 MEDLINE
DOCUMENT NUMBER: 21449695 PubMed ID: 11566017
TITLE: GM-611 (Chugai Pharmaceutical).
AUTHOR: Peeters T L
CORPORATE SOURCE: Gasthuisberg ON, Gut Hormone Laboratory, Leuven, Belgium.. theo.peeters@med.kuleuven.ac.be
SOURCE: Curr Opin Investig Drugs, (2001 Apr) 2 (4) 555-7. Ref: 23
Journal code: 100965718. ISSN: 1472-4472.
PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20020122
Entered Medline: 20011204

AB GM-611 is an erythromycin derivative that acts as an agonist at the **motilin receptor.** It is being developed by Chugai as a potential treatment for gastric motility disorder [169036], as well as reflux esophagitis, non-ulcer dyspepsia and diabetic gastroparesis [347963]. GM-611 is in phase II trials in the US for reflux esophagitis [322624], [347955], [399349]. GM-611 acts by a novel mechanism whereby it stimulates and promotes peristalsis in the stomach and other segments of the gastrointestinal tract [334994]. The drug was shown to produce a dose-dependent sustained depolarization of rabbit duodenal smooth muscle. Depolarization appeared to be associated with activation of monovalent cation-selective channels [273336]. In December 2000, Credit Suisse First Boston predicted that successful development of GM-611 could lead to sales over $500 million [400228].

L19 ANSWER 82 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001386523 EMBASE
TITLE: Nonulcer dyspepsia.
AUTHOR: Hammer J.; Talley N.J.
CORPORATE SOURCE: Dr. N.J. Talley, Department of Medicine, University of Sydney, Nepean Hospital, P.O. Box 63, Penrith, NSW 2751, Australia
SOURCE: Current Opinion in Gastroenterology, (2001) 17/6 (518-522). Refs: 30
ISSN: 0267-1379 CODEN: COGAEK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Therapy for nonulcer dyspepsia has largely been empiric because effective therapeutic agents are sparse and therapeutic trials show inconsistent results. The Cochrane collaboration has reviewed this matter and came to the conclusion that prokinetics and acid-suppression therapy might have a significant, although small, clinical benefit over placebo. Although the role of Helicobacter pylori in nonulcer dyspepsia is still a matter of controversy, one meta-analysis suggests that in H. pylori-positive dyspeptic patients, H. pylori eradication has a small but significant therapeutic benefit over a therapy that does not eradicate H. pylori. Other aspects of pathophysiology of nonulcer dyspepsia that have been studied in the past year include visceral hyperalgesia and abnormal sleep pattern. New studies have also investigated the clinical presentation of nonulcer dyspepsia and the possible reasons why some patients never consult a doctor whereas others do so frequently. .COPYRGT. 2001 Lippincott Williams & Wilkins, Inc.

L19 ANSWER 83 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2002086246 MEDLINE
DOCUMENT NUMBER: 21672960 PubMed ID: 11813507
TITLE: Motilin and **motilin receptors**: characterization and functional significance.
AUTHOR: Depoortere I

CORPORATE SOURCE: Centrum voor Gastro-enterologisch Onderzoek Laboratorium voor Gastro-intestinale Hormonen KULeuven, Faculteit Geneeskunde Gasthuisberg, O&N Herestraat 49-B-3000 Leuven.
SOURCE: VERHANDELINGEN - KONINKLIJKE ACADEMIE VOOR GENEESKUNDE VAN BELGIE, (2001) 63 (6) 511-29. Ref: 53
Journal code: 0413210. ISSN: 0302-6469.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020130
Last Updated on STN: 20020213
Entered Medline: 20020212

AB In order to get more insight into the mechanism of action of the gastrointestinal peptide, motilin, and its role in human physiology, we aimed at characterizing motilin and **motilin receptors.**
Motilin. Sequence analysis of the motilin precursor from several species indicated that the N- and C-terminal regions of the motilin precursor have evolved at different rates. Sequence analysis of the motilin precursor in brain tissue of rabbit and man and motilin radioimmunoassay on tissue extracts, proved that motilin is a brain-gut peptide. Plasma motilin levels are increased in patients with ulcerative colitis or Crohn's disease. A weak correlation between the motilin genotype and the susceptibility to inflammatory bowel disease was demonstrated.
Motilin receptors. Motilin receptors are expressed early postnatally and can be regulated by changes in its plasma level. The pharmacophore of motilin consists of the aromatic rings from Phe1 and Tyr7 and the aliphatic side chains from Val2 and Ile4. In vivo and in vitro studies showed that in the rabbit and human antrum, smooth muscle and neuronal **motilin receptors** exist which have different characteristics. In the rabbit duodenum motilin's action depends upon the influx of extra- and intracellular Ca2+. Nevertheless, in primary smooth muscle cultures, Ca2+ influx through L-type Ca2+ channels is the major transduction mechanism. The existence of central **motilin receptors** was demonstrated by autoradiography. Receptor binding studies allowed the identification of two binding sites. In contrast to antral smooth muscle cells, the response to motilin in the human TE671 medulloblastoma cell line, expressing the **motilin receptor**, relies on intracellular IP3-sensitive Ca2+ stores. The antibiotic erythromycin-A (EM-A) binds to the **motilin receptor** and induces contractions with the same regional and species specificity as motilin. This interaction was supported by the discovery of motilin antagonists. Structure activity studies led to the development of more powerful erythromycin derivatives, which lack antibiotic properties and which are now in clinical trial for treatment of hypomotility disorders. Conclusion and perspectives. The physiological role of motilin and its receptors in the brain requires further investigation. Erythromycin and its derivatives act as motilin agonists with clinically useful prokinetic potential. The **motilin receptor** has recently been cloned and has substantial structural homology with the growth hormone secretagogue receptor. This may not only lead to the further characterization of **motilin receptor** subtypes and aid the development of safe and selective **motilin receptor** agonists and antagonists, useful for the treatment of GI disorders, but may also give a new dimension to the role of motilin in human physiology.

L19 ANSWER 84 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:500433 SCISEARCH
THE GENUINE ARTICLE: 429KA
TITLE: Exploration of the peptide ligand-binding domain of the **motilin receptor** using photoaffinity

labeling and receptor mutagenesis
AUTHOR: Matsuura B (Reprint); Dong M Q; Coulie B; Hadac E M; Pinon D I; Onji M; Miller L J
CORPORATE SOURCE: Mayo Clin, Rochester, MN USA; Ehime Univ, Matsuyama, Ehime, Japan
COUNTRY OF AUTHOR: USA; Japan
SOURCE: GASTROENTEROLOGY, (APR 2001) Vol. 120, No. 5, Supp. [1], pp. A509-A509. MA 2591.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 85 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:500220 SCISEARCH
THE GENUINE ARTICLE: 429KA
TITLE: GM-611, a **motilin-receptor** agonist, accelerates gastric emptying in patients with symptomatic gastroparesis
AUTHOR: Fang J (Reprint); McCallum R; Kipnes M K; Tougas G; Miner P B; Dibaise J K; Schmitt C M; Abell T L; Clinkingbeard C; Hardi R; Verne N; Pertschuk D
CORPORATE SOURCE: Salt Lake City VA Med Ctr, Salt Lake City, UT USA; Univ Kansas, Med Ctr, Kansas City, KS 66103 USA; Diabet & Glandular Dis Clin, San Antonio, TX USA; McMaster Univ, Med Ctr, Hamilton, ON, Canada; Oklahoma Fdn Digest Res, Oklahoma City, OK USA; Univ Nebraska, Med Ctr, Omaha, NE USA; SE Clin Res, Chattanooga, TN USA; Univ Tennessee, Memphis, TN USA; Metropolitan Gastroenterol Grp, Chevy Chase, MD USA; VA Med Ctr, Dept Gastroenterol 111C, Gainesville, FL USA; Chugai Biopharmaceut Inc, San Diego, CA USA
COUNTRY OF AUTHOR: USA; Canada
SOURCE: GASTROENTEROLOGY, (APR 2001) Vol. 120, No. 5, Supp. [1], pp. A467-A467. MA 2375.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 86 OF 391 MEDLINE on STN DUPLICATE 34
ACCESSION NUMBER: 2001466541 MEDLINE
DOCUMENT NUMBER: 21402615 PubMed ID: 11511562
TITLE: Effects of a **motilin receptor** agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: a randomised, double blind, placebo controlled trial.
COMMENT: Comment in: Gut. 2001 Sep;49(3):317-8
Comment in: Gut. 2002 Oct;51(4):612; author reply 612-3
AUTHOR: Talley N J; Verlinden M; Geenen D J; Hogan R B; Riff D; McCallum R W; Mack R J
CORPORATE SOURCE: Department of Medicine, University of Sydney, Nepean Hospital, Penrith NSW, Australia.
SOURCE: GUT, (2001 Sep) 49 (3) 395-401.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010821
Last Updated on STN: 20010924
Entered Medline: 20010920

AB INTRODUCTION: Erythromycin, a motilin agonist, is a potent prokinetic. ABT-229 is a specific motilin agonist that dose dependently accelerates gastric emptying. Dyspepsia and gastroparesis are common problems in type 1 diabetes mellitus. We aimed to evaluate the efficacy of ABT-229 in symptomatic diabetic patients with and without delayed gastric emptying. METHODS: Patients with type 1 diabetes and postprandial symptoms were randomised (n=270). Based on a validated C(13) octanoic acid breath test, patients were assigned to either the delayed or normal gastric emptying strata. Patients received one of four doses of ABT-229 (1.25, 2.5, 5, or 10 mg twice daily before breakfast and dinner) or placebo for four weeks following a two week baseline. A self report questionnaire measured symptoms on visual analogue scales; the primary outcome was assessment of change in the total upper abdominal symptom severity score (range 0-800 mm) from baseline to the final visit. RESULTS: The treatment arms were similar regarding baseline characteristics. There was symptom improvement on placebo and a similar level of improvement on active therapy for the upper abdominal discomfort severity score (mean change from baseline -169, -101, -155, -143, and -138 mm for placebo, and 1.25, 2.5, 5, and 10 mg ABT-229, respectively, at four weeks by intent to treat). The results were not significantly different in those with and without delayed gastric emptying. The severity of bloating, postprandial nausea, epigastric discomfort, heartburn, and acid regurgitation worsened dose dependently in a greater number of patients receiving ABT-229 than placebo. Overall, 63% of patients on placebo reported a good or excellent global response, and this was not different from the active treatment arms. CONCLUSIONS: The motilin agonist ABT-229 was not efficacious in the relief of postprandial symptoms in diabetes mellitus in the presence or absence of delayed gastric emptying.

L19 ANSWER 87 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 35
ACCESSION NUMBER: 2002:158027 BIOSIS
DOCUMENT NUMBER: PREV200200158027
TITLE: Lack of molecular evidence for **motilin receptor** (GPR-38) subtypes in GI tract and CNS.
AUTHOR(S): Yan, Mujing [Reprint author]; Madireddi, Malavi; Gray, Kevin; Sasseville, Vito; Gordon, David
CORPORATE SOURCE: Hopewell Biology, Bristol-Myers Squibb Co., 311 Pennington-Rocky Hill Rd., Pennington, NJ, 08502, USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 360a. print.
Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology. Washington DC, USA. December 08-12, 2001. American Society for Cell Biology.
CODEN: MBCEEV. ISSN: 1059-1524.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

L19 ANSWER 88 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2001180625 MEDLINE
DOCUMENT NUMBER: 21100066 PubMed ID: 11159873
TITLE: Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin.
AUTHOR: Asakawa A; Inui A; Kaga T; Yuzuriha H; Nagata T; Ueno N; Makino S; Fujimiya M; Niijima A; Fujino M A; Kasuga M
CORPORATE SOURCE: Second Department of Internal Medicine, Kobe University School of Medicine, Kobe, Japan.

SOURCE: GASTROENTEROLOGY, (2001 Feb) 120 (2) 337-45.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB BACKGROUND & AIMS: : Ghrelin, an endogenous ligand for growth hormone secretagogue receptor, was recently identified in the rat stomach. We examined the effects of the gastric peptide ghrelin on energy balance in association with leptin and vagal nerve activity. METHODS: : Food intake, oxygen consumption, gastric emptying, and hypothalamic neuropeptide Y (NPY) messenger RNA expression were measured after intra-third cerebroventricular or intraperitoneal injections of ghrelin in mice. The gastric vagal nerve activity was recorded after intravenous administration in rats. Gastric ghrelin gene expression was assessed by Northern blot analysis. Repeated coadministration of ghrelin and interleukin (IL)-1 beta was continued for 5 days. RESULTS: : Ghrelin exhibited gastroprokinetic activity with structural resemblance to motilin and potent orexigenic activity through action on the hypothalamic neuropeptide Y (NPY) and Y(1) receptor, which was lost after vagotomy. Ghrelin decreased gastric vagal afferent discharge in contrast to other anorexigenic peptides that increased the activity. Ghrelin gene expression in the stomach was increased by fasting and in ob/ob mice, and was decreased by administration of leptin and IL-1 beta. Peripherally administered ghrelin blocked IL-1 beta-induced anorexia and produced positive energy balance by promoting food intake and decreasing energy expenditure. CONCLUSIONS: : Ghrelin, which is negatively regulated by leptin and IL-1 beta, is secreted by the stomach and increases arcuate NPY expression, which in turn acts through Y(1) receptors to increase food intake and decrease energy expenditure. Gastric peptide ghrelin may thus function as part of the orexigenic pathway downstream from leptin and is a potential therapeutic target not only for obesity but also for anorexia and cachexia.

L19 ANSWER 89 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:479329 BIOSIS
DOCUMENT NUMBER: PREV200100479329
TITLE: What comes after macrolides and other motilin stimulants?.
AUTHOR(S): Tack, J. [Reprint author]; Peeters, T.
CORPORATE SOURCE: Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium
Jan.Tack@med.kuleuven.ac.be
SOURCE: Gut, (September, 2001) Vol. 49, No. 3, pp. 317-318. print.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Oct 2001
Last Updated on STN: 23 Feb 2002

L19 ANSWER 90 OF 391 MEDLINE on STN DUPLICATE 36
ACCESSION NUMBER: 2002023951 MEDLINE
DOCUMENT NUMBER: 21362401 PubMed ID: 11469754
TITLE: Discovery of the first non-peptide antagonist of the **motilin receptor.**
AUTHOR: Beavers M P; Gunnet J W; Hageman W; Miller W; Moore J B; Zhou L; Chen R H; Xiang A; Urbanski M; Combs D W; Mayo K H; Demarest K T
CORPORATE SOURCE: The R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ 08869, USA.

SOURCE: DRUG DESIGN AND DISCOVERY, (2001) 17 (3) 243-51.
Journal code: 9200627. ISSN: 1055-9612.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011207

AB A first-in-class non-peptide antagonist of the **motilin receptor** was identified through electronic screening of our corporate database against a 3D pharmacophore. The pharmacophore was developed from the motilin 22 residue endogenous peptide using NMR structural data, principles of peptide folding, and peptide structure activity relationships. The NMR data supported helical content within the peptide, and both the hydrophobic staple and N-capping box motifs were identified in the motilin sequence. The conformational features of these motifs were imposed on the peptide structure, providing a constrained conformer as a starting point for database searching. A trisubstituted cyclopentene lead was identified directly from the electronic search. Compounds in this series inhibit the binding of 125I-motilin to human antral smooth muscle membrane and antagonize motilin-induced intracellular calcium mobilization in cells expressing the human **motilin receptor.** A potent compound developed through optimization, RWJ 68023, is active in binding and cell-based functional assays and is also effective in inhibiting motilin-induced contractility in segments of rabbit duodenum. This orally active compound is currently undergoing clinical evaluation for the treatment of gastrointestinal disorders associated with altered motility.

L19 ANSWER 91 OF 391 MEDLINE on STN DUPLICATE 37
ACCESSION NUMBER: 2001161530 MEDLINE
DOCUMENT NUMBER: 21159514 PubMed ID: 11259768
TITLE: Demonstration of a functional **motilin receptor** in TE671 cells from human cerebellum.
AUTHOR: Thielemans L; Depoortere I; Van Assche G; Bender E; Peeters T L
CORPORATE SOURCE: Gut Hormone Laboratory, Center for Gastroenterological Research, Department of Pathophysiology, Katholieke Universiteit Leuven, Gasthuisberg O & N, Herestraat 49, Leuven B-3000, Belgium.
SOURCE: BRAIN RESEARCH, (2001 Mar 23) 895 (1-2) 119-28.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB BACKGROUND: Our laboratory has described the presence of **motilin receptors** in the rabbit cerebellum. We discovered its presence in the human TE671 cell line, which is of cerebellar origin. METHODS: Cytosolic Ca(2+) fluxes were monitored on a confocal microscope in cells loaded with Indo-1 and stimulated with motilin under various conditions. Binding studies were performed with 125I-[Nle(13)]porcine motilin. Using primers, PCR for the **motilin receptor** was performed. RESULTS: Cells responded to motilin after 45+/-20 s. At different concentrations of motilin (10(-8), 10(-7), 10(-6.5), 10(-6) and 10(-5) M) the percentage of responding cells was 0+/-0, 0.6+/-1.5, 4.9+/-4.7, 21.7+/-15 and 35.7+/-12, respectively. The response was blocked by the motilin antagonists [Phe(3), Nle(13)]po-motilin (0.8+/-1.8%) and GM-109 (0.0+/-0.0%) and mimicked by the agonist ABT-229 (23.6+/-15%). After

stimulation with motilin, ABT-229 or [Phe(3),Leu(13)]po-motilin, but not with the antagonist GM-109, cells were desensitized. The response to motilin persisted in Ca(2+)-free solution (22.8+/-14.7%), was not affected by nifedipine (44+/-11%) but was abolished by incubation with thapsigargin (0+/-0%). Neither ryanodine, nor a previous stimulation with caffeine (0+/-0%) in Ca(2+)-free Krebs, nor both could block the response to motilin (28, 32.0+/-5.7, 41.3+/-6.1%, respectively). Binding studies revealed two binding sites for motilin, with a pK(d) of 8.9+/-0.05 and 6.11+/-0.61 (n=4). There were 100 times more low than high affinity receptors per cell. The presence of receptor mRNA was confirmed by PCR. CONCLUSION: Functional **motilin receptors** are present in TE671 cells. The response requires intracellular IP(3)-sensitive Ca(2+) stores. These cells may serve as a model of the central **motilin receptor.**

L19 ANSWER 92 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2001384558 MEDLINE
DOCUMENT NUMBER: 21331552 PubMed ID: 11438309
TITLE: The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound.
AUTHOR: Briejer M R; Bosmans J P; Van Daele P; Jurzak M; Heylen L; Leysen J E; Prins N H; Schuurkes J A
CORPORATE SOURCE: Department of Gastrointestinal Pharmacology, Janssen Research Foundation, Turnhoutseweg 30, 2340 Beerse, Belgium.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2001 Jun 29) 423 (1) 71-83.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830

AB Prucalopride is a novel enterokinetic compound and is the first representative of the benzofuran class. We set out to establish its pharmacological profile in various receptor binding and organ bath experiments. Receptor binding data have demonstrated prucalopride's high affinity to both investigated 5-HT(4) receptor isoforms, with mean pK(i) estimates of 8.60 and 8.10 for the human 5-HT(4a) and 5-HT(4b) receptor, respectively. From the 50 other binding assays investigated in this study only the human D(4) receptor (pK(i) 5.63), the mouse 5-HT(3) receptor (pK(i) 5.41) and the human sigma(1) (pK(i) 5.43) have shown measurable affinity, resulting in at least 290-fold selectivity for the 5-HT(4) receptor. Classical organ bath experiments were done using isolated tissues from the rat, guinea-pig and dog gastrointestinal tract, using various protocols. Prucalopride was a 5-HT(4) receptor agonist in the guinea-pig colon, as it induced contractions (pEC(50)=7.48+/-0.06; insensitive to a 5-HT(2A) or 5-HT(3) receptor antagonist, but inhibited by a 5-HT(4) receptor antagonist) as well as the facilitation of electrical stimulation-induced noncholinergic contractions (blocked by a 5-HT(4) receptor antagonist). Furthermore, it caused relaxation of a rat oesophagus preparation (pEC(50)=7.81+/-0.17), in a 5-HT(4) receptor antagonist sensitive manner. Prucalopride did not cause relevant inhibition of 5-HT(2A), 5-HT(2B), or 5-HT(3), motilin or cholecystokinin (CCK(1)) receptor-mediated contractions, nor nicotinic or muscarinic acetylcholine receptor-mediated contractions, up to 10 microM. It is concluded that prucalopride is a potent, selective and specific 5-HT(4) receptor agonist. As it is intended for treatment of intestinal motility disorders, it is important to note that prucalopride is devoid of anti-cholinergic, anticholinesterase or nonspecific inhibitory activity and does not antagonise 5-HT(2A), 5-HT(2B) and 5-HT(3) receptors or motilin or CCK(1) receptors.

L19 ANSWER 93 OF 391 MEDLINE on STN DUPLICATE 38
ACCESSION NUMBER: 2001195513 MEDLINE
DOCUMENT NUMBER: 21110120 PubMed ID: 11169126
TITLE: **Motilin receptor** density in inflamed and noninflamed tissue in rabbit TNBS-induced colitis.
AUTHOR: Depoortere I; Van Assche G; Peeters T L
CORPORATE SOURCE: Centre for Gastroenterological Research, Department of Pathophysiology, University of Leuven, B-3000 Leuven, Belgium.
SOURCE: NEUROGASTROENTEROLOGY AND MOTILITY, (2001 Feb) 13 (1) 55-63.
Journal code: 9432572. ISSN: 1350-1925.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

AB Trinitrobenzenesulphonic acid (TNBS)-induced colitis decreases the contractile response of the rabbit colon to motilin, and inflammation may increase plasma motilin levels. We studied whether the decreased contractility could be due to a down-regulation of **motilin receptors**, caused by increased plasma motilin levels. As this would affect all tissues, uninflamed sites were studied as well. Colitis was induced by different doses (100-150 mg kg-1) of TNBS. In the colon, the TNBS dose-dependent decrease of the contractile response towards motilin was reflected in a decrease in **motilin receptor** density. In contrast, in the antrum, receptors were upregulated by 150 mg kg-1 TNBS, while central **motilin receptors** in the cerebellum were not affected. Plasma motilin levels were not influenced by inflammation, although the motilin content and mRNA expression in the duodenal and jejunal mucosa, but not in the colon, was significantly increased. The opposite was true for interleukin-1beta and interleukin receptor antagonist mRNA expression. We conclude that the decreased motilin contractility in rabbit colitis is due to a downregulation of **motilin receptors** in the colon, but this is not caused by chronic hormonal stimulation.

L19 ANSWER 94 OF 391 MEDLINE on STN DUPLICATE 39
ACCESSION NUMBER: 2001177746 MEDLINE
DOCUMENT NUMBER: 21042031 PubMed ID: 11201222
TITLE: Design and synthesis of N-terminal cyclic motilin partial peptides: a novel pure motilin antagonist.
AUTHOR: Haramura M; Okamachi A; Tsuzuki K; Yogo K; Ikuta M; Kozono T; Takanashi H; Murayama E
CORPORATE SOURCE: Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co. Ltd., Shizuoka, Japan.. mharamura@chugaibio.com
SOURCE: CHEMICAL AND PHARMACEUTICAL BULLETIN, (2001 Jan) 49 (1) 40-3.
Journal code: 0377775. ISSN: 0009-2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB Motilin antagonist was designed and synthesized on the basis of the structure-activity relationship analysis of porcine motilin that we reported recently. The drug design was performed on a specific concept to reduce a flexibility of peptide conformation of porcine motilin partial

peptide by its cyclization. The cyclic peptide was synthesized using Boc (tert-butyloxycarbonyl) solid phase methodology, followed by cyclization using the azide procedure, and tested for the binding activity to **motilin receptor** and smooth muscle contractile activity. The cyclic peptides 3, 4, and 5 showed antagonistic property on contraction assay (pA2 [the negative logarithm of molar concentration of antagonist causing a 2-hold shift to the right of the concentration-response curve for motilin]: 4.5, 4.34, and 4.04, respectively, in rabbit duodenum) and no contractile activity even at high concentration.

L19 ANSWER 95 OF 391 MEDLINE on STN DUPLICATE 40
ACCESSION NUMBER: 2001195510 MEDLINE
DOCUMENT NUMBER: 21110117 PubMed ID: 11169123
TITLE: Contractile effects and intracellular Ca2+ signalling induced by motilin and erythromycin in the circular smooth muscle of human colon.
AUTHOR: Van Assche G; Depoortere I; Thijs T; Missiaen L; Penninckx F; Takanashi H; Geboes K; Janssens J; Peeters T L
CORPORATE SOURCE: Center for Gastroenterological Research, University of Leuven, B-3000 Leuven, Belgium.
SOURCE: NEUROGASTROENTEROLOGY AND MOTILITY, (2001 Feb) 13 (1) 27-35.
Journal code: 9432572. ISSN: 1350-1925.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

AB Motilin has excitatory effects on the colon of the rabbit and the dog, but little is known of its effect on the human colon. The aim of this study was to investigate the effects induced by motilin and erythromycin A (EMA) on muscle strips and on single cells from primary cultures from human colon. Isotonic contraction was recorded in circular muscle strips from macroscopically normal resection specimens of patients operated on for colonic neoplasm. Agonist-induced intracellular Ca2+ ([Ca2+]i) signalling was studied in primary cultures of colonic smooth-muscle cells using the ratiometric Ca2+ indicator Indo 1, on a laser-scanning confocal epifluorescence microscope. In circular muscle strips, norleucine13-porcine motilin ([Nle13]-pm)and EMA induced tonic contractions with an EC50 of 92 +/- 21 nmol L(-1) and 31 +/- 16 micromol L(-1), respectively. The maximal contraction was 21 +/- 4% (motilin) and 33 +/- 12% (EMA) of the response to 10(-4) mol L(-1) acetylcholine (ACh). The motilin antagonist OHM-11526 (10(-5.5) mol L(-1)) abolished the effects of both [Nle13]-pm and EMA. Neither tetrodotoxin (10(-5.5) mol L(-1)), L-nitro-D-arginine methyl ester (L-NAME) (10(-3.5) mol L(-1)) nor guanethidine (10(-5) mol L(-1)) interfered with the effects of [Nle13]-pm or EMA. [Nle13]-pm (10(-11)-10(-6) mol L(-1)) induced rises of [Ca2+]i in cultured colonic myocytes. At 10(-6) mol L-1, 94% of the cells responded, and half of the cells responded at 1.4 nmol L(-1) [Nle13]-pm. 81% (35/43) and 95% (75/79) responded to EMA (10(-6) mol L(-1)) and acetylcholine (ACh, 10(-4) mol L(-1)), respectively. The motilin antagonist GM-109 inhibited motilin- and EMA-induced [Ca2+]i rises. In the absence of extracellular Ca2+, only 13% (7/52) of the cells responded to [Nle13]-pm (10(-6) mol L(-1)) vs. 90% (47/52) to ACh (10(-4) mol L(-1)). Motilin and EMA have direct excitatory effects on circular smooth muscle from the human colon and these effects are mediated via a smooth-muscle **motilin receptor.** These findings suggest that motilin may regulate colonic motility and that motilides may have therapeutic potential for the treatment of colonic hypomotility.

L19 ANSWER 96 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:188045 BIOSIS

DOCUMENT NUMBER: PREV200200188045
TITLE: Circulating ghrelin levels are decreased by food intake and correlate with gastric emptying time.
AUTHOR(S): Wawarta, Rainer [Reprint author]; Riepl, Rudolf [Reprint author]; Tschoep, Matthias [Reprint author]; Folwaczny, Christian [Reprint author]
CORPORATE SOURCE: Innenstadt Univ Hosp, Munich, Germany
SOURCE: Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.172-A.173. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

L19 ANSWER 97 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:201108 BIOSIS
DOCUMENT NUMBER: PREV200200201108
TITLE: Exploration of the peptide ligand-binding domain of the **motilin receptor** using photoaffinity labeling and receptor mutagenesis.
AUTHOR(S): Matsuura, Bunzo [Reprint author]; Dong, Maoqing [Reprint author]; Coulie, Bernard [Reprint author]; Hadac, Elizabeth M. [Reprint author]; Pinon, Delia I. [Reprint author]; Onji, Morikazu; Miller, Laurence J.
CORPORATE SOURCE: Mayo Clin, Rochester, MN, USA
SOURCE: Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.509. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002

L19 ANSWER 98 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:200900 BIOSIS
DOCUMENT NUMBER: PREV200200200900
TITLE: GM-611, a **motilin-receptor** agonist, accelerates gastric emptying in patients with symptomatic gastroparesis (GP).
AUTHOR(S): Fang, John [Reprint author]; McCallum, Richard; Kipnes, Mark K.; Tougas, Gervais; Miner, Philip B., Jr.; DiBaise, John K.; Schmitt, Colleen M.; Abell, Thomas L.; Clinkingbeard, Cynthia; Hardi, Robert; Verne, G. Nicholas; Pertschuk, Daniel
CORPORATE SOURCE: Salt Lake City VA Medical Centers, Salt Lake City, UT, USA
SOURCE: Gastroenterology, (April, 2001) Vol. 120, No. 5 Supplement 1, pp. A.467. print.
Meeting Info.: 102nd Annual Meeting of the American

Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002

L19 ANSWER 99 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2000173327 MEDLINE
DOCUMENT NUMBER: 20173327 PubMed ID: 10710093
TITLE: Erythromycin eye ointment: effect on gastrointestinal motility.
AUTHOR: Moussa F; Alaswad B; Garcia J
SOURCE: AMERICAN JOURNAL OF GASTROENTEROLOGY, (2000 Mar) 95 (3) 826.
Journal code: 0421030. ISSN: 0002-9270.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000321

L19 ANSWER 100 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 41
ACCESSION NUMBER: 2000-543364 [49] WPIDS
DOC. NO. CPI: C2000-161638
TITLE: New phenethylamine derivatives are **motilin receptor** antagonists useful for treating e.g. Crohn's disease, ulcerative colitis and diabetes.
DERWENT CLASS: B05
INVENTOR(S): JUNG, K Y; KIM, D I; MATSUOKA, H; PARK, C H; SATO, T; TAKAHASHI, T; PARK, C
PATENT ASSIGNEE(S): (CHUS) CHUGAI SEIYAKU KK; (CHUS) CHUGAI PHARM CO LTD
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000044770	A1	20000803	(200049)*	JA	403
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000023203	A	20000818	(200057)		
NO 2001003684	A	20010928	(200170)		
EP 1149843	A1	20011031	(200172)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
KR 2001101750	A	20011114	(200230)		
JP 2000596026	X	20020521	(200236)		
HU 2001005204	A2	20020429	(200238)		
CN 1343219	A	20020403	(200247)		
CZ 2001002714	A3	20020814	(200263)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000044770	A1	WO 2000-JP444	20000128
AU 2000023203	A	AU 2000-23203	20000128
NO 2001003684	A	WO 2000-JP444	20000128
		NO 2001-3684	20010726
EP 1149843	A1	EP 2000-901956	20000128
		WO 2000-JP444	20000128
KR 2001101750	A	KR 2001-709475	20010727
JP 2000596026	X	JP 2000-596026	20000128
		WO 2000-JP444	20000128
HU 2001005204	A2	WO 2000-JP444	20000128
		HU 2001-5204	20000128
CN 1343219	A	CN 2000-804822	20000128
CZ 2001002714	A3	WO 2000-JP444	20000128
		CZ 2001-2714	20000128

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000023203	A	Based on	WO 2000044770
EP 1149843	A1	Based on	WO 2000044770
JP 2000596026	X	Based on	WO 2000044770
HU 2001005204	A2	Based on	WO 2000044770
CZ 2001002714	A3	Based on	WO 2000044770

PRIORITY APPLN. INFO: JP 1999-283163 19991004; JP 1999-20523 19990128

AN 2000-543364 [49] WPIDS

AB WO 200044770 A UPAB: 20001006

NOVELTY - Phenethylamine derivatives (I) are new.

DETAILED DESCRIPTION - Phenethylamine derivatives of formula (I) and their hydrates and salts are new.

Cy = phenyl (optionally substituted by 1-5 R), optionally substituted heterocyclyl or 3-7C cycloalkyl;

at least one of R = halo, CF3 or nitrile; and

the others = OH or NH2;

R6 = H, optionally substituted 1-3C alkyl, NH2 or OH;

R7 = H, OH or optionally substituted 1-3C alkyl or amino;

R8 = H, Me or Et;

R9 = 3-7C cycloalkyl or optionally substituted 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl or phenyl;

R20 = H or 1-3C alkyl; or

CR9R20 = 3-7C cycloalkyl;

R10 = H or 1-3C alkyl;

R11 = H, 1-3C alkyl, CONR14R15, COOH or optionally substituted heterocyclyl;

R12 = H or OR16;

R13 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl or CR17R18R19;

R14, R15 = H, 1-4C alkyl, 3-7C cycloalkyl, 1-4C alkoxy, 1-4C alkylsulfonyl or heterocyclyl; or

NR14R15 = optionally substituted 3-7 membered cycloamino;

R16 = 1-4C alkyl;

R17 = H or Me;

R18+R19 = 3-7C cycloalkyl or cycloalkenyl;

X, Y = CO or CH2;

provided that when (a) Cy is 3-indolyl then (i) R11 is optionally substituted heterocyclyl; or (ii) R6 = H, R7 = amino, R8, R10 = Me, R9 = isopropyl, R20 = H, R11 = carbamoyl, R12 = OH, R13 = t-butyl and X, Y = CO; or (b) Cy = cyclohexyl or phenyl, then R11 is optionally substituted heterocyclyl.

INDEPENDENT CLAIMS are also included for intermediates of formula

(IV) and (VI)-(X) and their salts.
R71, R111 = optionally protected R7 and R11 respectively;
P1 = H or amino protecting group;
P2 = optionally protected carboxy, CHO or a group which is removed to give Me.
ACTIVITY - Gastrointestinal-Gen.; Antiinflammatory; Antiulcer; Antidiabeic; Anorectic.
MECHANISM OF ACTION - Motilin-Antagonist.
In a motilin binding assay, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-t-Bu)-NHEt had an IC50 value of 0.17 nM.
USE - As motilin receptor antagonists and for reducing blood motilin levels useful for treating or preventing Crohn's disease, ulcerative colitis, pancreatitis, diabetes, obesity, irritable bowel syndrome, malabsorption of nutrients, microflora imbalance, gastric blockage and atrophic gastritis.
Dwg.0/0

L19 ANSWER 101 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 42

ACCESSION NUMBER: 2000-283541 [24] WPIDS
DOC. NO. CPI: C2000-085653
TITLE: New ethylamine derivatives are **motilin receptor** antagonists useful for treating e.g. gastric motility disorders.
DERWENT CLASS: B03
INVENTOR(S): MATSUOKA, H; SATO, T
PATENT ASSIGNEE(S): (CHUS) CHUGAI SEIYAKU KK; (CHUS) CHUGAI PHARM CO LTD
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000017231	A1	20000330	(200024)*	JA	101
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 9957592	A	20000410	(200035)		
EP 1116726	A1	20010718	(200142)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2000574139	X	20011211	(200213)		
KR 2001085842	A	20010907	(200218)		
US 6586630	B1	20030701	(200345)		
TW 509699	A	20021111	(200353)		
US 2003176643	A1	20030918	(200362)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000017231	A1		WO 1999-JP5215	19990924
AU 9957592	A		AU 1999-57592	19990924
EP 1116726	A1		EP 1999-944808	19990924
			WO 1999-JP5215	19990924
JP 2000574139	X		WO 1999-JP5215	19990924
			JP 2000-574139	19990924
KR 2001085842	A		KR 2001-703778	20010323
US 6586630	B1		WO 1999-JP5215	19990924
			US 2001-787674	20010321
TW 509699	A		TW 1999-116326	19990922
US 2003176643	A1	Div ex	WO 1999-JP5215	19990924
		Div ex	US 2001-787674	20010321

US 2003-356558 20030203

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9957592	A	Based on	WO 2000017231
EP 1116726	A1	Based on	WO 2000017231
JP 2000574139	X	Based on	WO 2000017231
US 6586630	B1	Based on	WO 2000017231

PRIORITY APPLN. INFO: JP 1998-307784 19980924
AN 2000-283541 [24] WPIDS
AB WO 200017231 A UPAB: 20000522
NOVELTY - Ethylamine derivatives (I) are new.
DETAILED DESCRIPTION - Ethylamine derivatives of formula (I) and their hydrates and salts are new.
R1 = 2-6C alkenyl, 2-6C alkynyl or optionally substituted phenyl or heterocyclyl;
R2 = H, amino, OH or optionally substituted 1-3C alkyl;
R3 = H, OH or optionally substituted amino or 1-3C alkyl;
R4, R6 = H, Me or Et;
R5 = 3-7C cycloalkyl or optionally substituted 1-6C alkyl or phenyl;
R7 = H, CONR9R10 or optionally substituted 1-3C alkyl;
R8 = optionally substituted 3-9C heterocyclyl or 3-R12, 4-R11-phenyl;
R9, R10 = H or 1-3C alkyl;
R11 = OH; and
R12 = 2-6C acyl, 1-5C alkylsulfonyl, amino (optionally mono or disubstituted by 1-5C alkyl) or substituted 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl; or
R11 = halo; and
R12 = 2-6C acyl, 1-5C alkylsulfonyl, amino (optionally mono or disubstituted by 1-5C alkyl) or optionally substituted 1-6C alkyl, 2-6C alkenyl or 2-6C alkynyl;
X, Y = CO or CH2.
ACTIVITY - Gastrointestinal; antiinflammatory.
MECHANISM OF ACTION - Motilin-Antagonist. Phe-N-Me-Val-Phe(3-tBu-4-F)-NH2 (Ia), diastereoisomer A had an IC50 of 3.5 nM for **motilin receptor** binding.
USE - As **motilin receptor** antagonists for treating or preventing gastric motility disorders and hypermotilinemia related disorders (claimed) such as irritable bowel syndrome.
Dwg.0/0

L19 ANSWER 102 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-365118 [31] WPIDS
CROSS REFERENCE: 1995-139540 [18]; 1997-052349 [05]; 1999-034664 [03]; 1999-142437 [12]; 2000-072618 [06]; 2000-610844 [58]; 2002-065495 [09]; 2003-041412 [03]; 2003-352291 [33]; 2003-897933 [82]
DOC. NO. CPI: C2000-110189
TITLE: New polyketide compounds, useful as agents having antibiotic and antiparasitic activity or for treating e.g. gastric disorders, gall bladder disorders or diabetics with autonomic neuropathy.
DERWENT CLASS: B03 C02 D16
INVENTOR(S): MCDANIEL, R
PATENT ASSIGNEE(S): (KOSA-N) KOSAN BIOSCIENCES INC
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000024907	A2	20000504	(200031)*	EN	36

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 2000014477 A 20000515 (200039)
EP 1124968 A2 20010822 (200149) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6403775 B1 20020611 (200244)
JP 2002528467 W 20020903 (200273) 56

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000024907	A2		WO 1999-US24483	19991020
AU 2000014477	A		AU 2000-14477	19991020
EP 1124968	A2		EP 1999-971039	19991020
			WO 1999-US24483	19991020
US 6403775	B1	Provisional	US 1998-105987P	19981028
			US 1999-429349	19991028
JP 2002528467	W		WO 1999-US24483	19991020
			JP 2000-578459	19991020

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000014477	A	Based on	WO 2000024907
EP 1124968	A2	Based on	WO 2000024907
JP 2002528467	W	Based on	WO 2000024907

PRIORITY APPLN. INFO: US 1998-105987P 19981028; US 1999-429349 19991028

AN 2000-365118 [31] WPIDS

CR 1995-139540 [18]; 1997-052349 [05]; 1999-034664 [03]; 1999-142437 [12]; 2000-072618 [06]; 2000-610844 [58]; 2002-065495 [09]; 2003-041412 [03]; 2003-352291 [33]; 2003-897933 [82]

AB WO 200024907 A UPAB: 20031223

NOVELTY - A library (I) of polyketide (PK) compounds is new.

DETAILED DESCRIPTION - (I) comprises a library of 61 compounds (given in the specification.

INDEPENDENT CLAIMS are also included for the following:

(1) a library of recombinant PKS genes comprising genes encoding PKs in (I);

(2) a library of host cells containing genes from (1);

(3) a library of PKs composed of PKs produced by contacting PKs as in (A) with a host cell selected from Saccharopolyspora erythraea Streptomyces venezuelae, S. narbonensis, S. antibioticus, S. fradiae, S. thermotolerans, and Micromonospora megalomicea; and

(4) the PKs 6-deoxy-12-norerythronolide B, 5,6-dideoxy-10-norerythronolide B, 2,10-bisnor-3-oxo-6-deoxy-10,11-anhydroerythronolide B, and 2,4-bisnor-3-oxo-6-deoxyerythronolide B, and the glycosylated and hydroxylated forms in pure form.

ACTIVITY - Antibiotic; antiparasitic; litholytic; hepatotropic; antidiabetic.

MECHANISM OF ACTION - Antibiotics; motilin agonist.

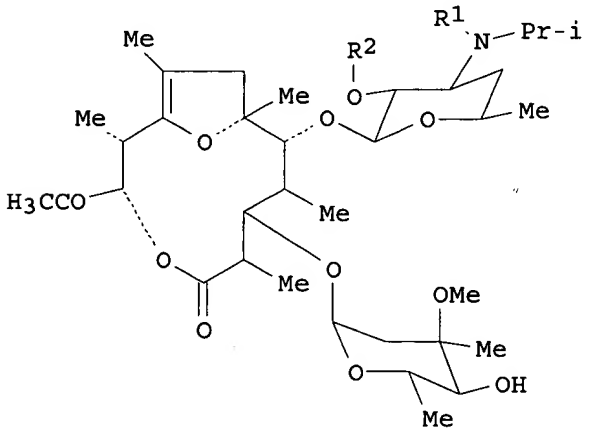
USE - The novel PKs are modified erythromycin compounds which can be used for treating diseases. The compounds can have antibiotic and antiparasitic activity. The compounds can also be used as motilides. They are potent agonists of the **motilin receptor** that can be used clinically as prokinetic agents to induce phase III of migrating motor complexes, to increase esophageal peristalsis and LES pressure in patients with GERD, to accelerate gastric emptying in patients with gastric paresis, and to stimulate gall bladder contractions in patients after gallstone removal and in diabetics with autonomic neuropathy.

Dwg.0/9

L19 ANSWER 103 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:909205 CAPLUS
DOCUMENT NUMBER: 134:42386
TITLE: Preparation and gastrointestinal tract properties of 11-acetyl-12,13-dioxabicyclo[8.2.1]-tridecenone derivatives of erythromycin antibiotics
INVENTOR(S): Jasserand, Daniel; Preuschoff, Ulf; Eeckhout, Christian
PATENT ASSIGNEE(S): Solvay Pharmaceuticals G.m.b.H., Germany
SOURCE: U.S., 7 pp., Cont.-in-part of U. S. Ser. No. 247,605, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6165985	A	20001226	US 1999-338602	19990623
DE 19805822	A1	19990819	DE 1998-19805822	19980213

PRIORITY APPLN. INFO.: DE 1998-19805822 A 19980213
US 1999-247605 B2 19990210
OTHER SOURCE(S): MARPAT 134:42386
GI



I

AB Ring-contracted N-demethyl-N-isopropyl-erythromycin A derivs. I wherein R1 is hydrogen or Me, R2 is hydrogen or alkanoyl, were prepared and having a modified side chain and gastrointestinally effective motilin-agonistic properties. Thus, I (R1 = Me, R2 = H) was prepared and tested for the binding capacity to **motilin receptors** (pIC50 = 8.01) and in vivo determination of its effect on the stomach tone.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 104 OF 391 MEDLINE on STN DUPLICATE 43
ACCESSION NUMBER: 2001306286 MEDLINE
DOCUMENT NUMBER: 20537767 PubMed ID: 11086932
TITLE: Three-dimensional structure-activity relationship analysis between motilin and motilide using conformational analysis and a novel molecular superposing method.
AUTHOR: Gouda H; Sunazuka T; Omura S; Hirono S
CORPORATE SOURCE: School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan.

SOURCE: CHEMICAL AND PHARMACEUTICAL BULLETIN, (2000 Nov) 48 (11) 1835-7.
Journal code: 0377775. ISSN: 0009-2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB Motilide, an erythromycin derivative, has been shown to equal activity to that of motilin as an agonist at the **motilin receptor.** However, there is little information on the three-dimensional (3D) structure-activity relationship between these two molecules, largely because they have quite different structures. In this study, we applied a rational computational procedure consisting of conformational analysis and a novel superposing method to investigate the 3D structure-activity relationship between motilide and motilin. We propose common 3D structural features between these molecules, which may be important for their similar activity.

L19 ANSWER 105 OF 391 MEDLINE on STN DUPLICATE 44
ACCESSION NUMBER: 2001088198 MEDLINE
DOCUMENT NUMBER: 20571113 PubMed ID: 11121915
TITLE: Failure of a **motilin receptor** agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial.
AUTHOR: Talley N J; Verlinden M; Snape W; Beker J A; Ducrotte P; Dettmer A; Brinkhoff H; Eaker E; Ohning G; Miner P B; Mathias J R; Fumagalli I; Staessen D; Mack R J
CORPORATE SOURCE: Department of Medicine, University of Sydney, Nepean Hospital, Penrith NSW, Australia; Abbott Laboratories, Abbott Park Illinois, USA.. talley@pnc.com.au
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (2000 Dec) 14 (12) 1653-61.
Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB INTRODUCTION: **Motilin-receptor** agonists are prokinetics; whether they relieve the symptoms of functional dyspepsia is unknown. We aimed to test the efficacy of the motilin agonist ABT-229 in functional dyspepsia patients with and without delayed gastric emptying. METHODS: Patients were randomized with postprandial symptoms and documented functional dyspepsia by endoscopy (n=589 in intention-to-treat analysis). Patients were assigned to either the delayed or normal gastric emptying strata, based on a validated 13C octanoic acid breath test. Patients were then further randomized within each strata, to receive one of four doses of ABT-229 (1.25, 2. 5, 5 or 10 mg b.d. before breakfast and dinner) or placebo for 4 weeks, following a 2-week baseline. The primary outcome was the assessment of change in symptom severity over the 2 weeks from baseline to final visit, based on a self-report questionnaire measuring severity on visual analogue scales. RESULTS: Baseline characteristics across the treatment arms were very similar. No significant differences in the upper abdominal discomfort severity score (maximum 800 mm) were observed for any active treatment arm vs. placebo

(mean change from baseline -139, -141, -145, -160 and -134 mm for placebo, 1.25, 2.5, 5, and 10 mg, respectively, at 4 weeks by intention-to-treat). More patients on placebo reported a good or excellent global response than patients on 1.25 or 5 mg of active therapy (both $P < 0.05$). The results were very similar in those with and without delayed gastric emptying. Helicobacter pylori status did not predict response. Excluding patients with any baseline heartburn (total remaining n=240), ABT-229 10 mg was inferior to placebo in relief of upper abdominal discomfort. CONCLUSIONS: ABT-229 was of no value for relief of symptoms in functional dyspepsia, compared with placebo.

L19 ANSWER 106 OF 391 MEDLINE on STN DUPLICATE 45
ACCESSION NUMBER: 2000330748 MEDLINE
DOCUMENT NUMBER: 20330748 PubMed ID: 10869416
TITLE: Effect of novel motilide ABT-229 versus erythromycin and cisapride on gastric emptying in dogs.
AUTHOR: Cowles V E; Nellans H N; Seifert T R; Besecke L M; Segreti J A; Mohning K M; Faghih R; Verlinden M H; Wegner C D
CORPORATE SOURCE: Department of Integrative Pharmacology and Gastroenterology Venture, Abbott Laboratories, Abbott Park, IL, USA.. vcowles@depomedinc.com
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Jun) 293 (3) 1106-11.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000714

AB ABT-229 (8,9-anhydro-4"-deoxy-3'-N-desmethyl-3'-N-ethylerythromycin B-6,9-hemiacetal), a synthetic derivative of erythromycin (ERY) with no antibiotic activity, has been shown to bind to **motilin receptors** and stimulate contractile activity of the antrum and small intestine. The objective of this study was to determine the effect of ABT-229 on canine gastric emptying (GE) and contractile activity of the antrum and duodenum in response to a solid meal. Six beagles were used to determine GE of a solid meal and contractile activity in response to either vehicle, ABT-229 (0.17, 0.83, 2.5, or 5.0 microg/kg/min), ERY (33.3 microg/kg/min), or cisapride (CIS) (10 microg/kg/min). Lag (t(lag)), half-emptying (t(1/2)), and complete emptying (t(full)) times were determined. Contractile data were analyzed for motility index and gastroduodenal coordination. Compared with vehicle, ABT-229 dose dependently accelerated GE, t(lag) was decreased at the two highest doses, t(1/2) was decreased compared with vehicle at the three highest doses, and t(full) was decreased at all doses compared with vehicle. ERY also decreased t(1/2) and t(full), whereas CIS decreased all GE parameters. The slopes of the linear phase of GE curves for all drugs and doses were greater than those for vehicle. ABT-229 dose dependently increased the motility index as well as gastroduodenal coordination. ABT-229 (two highest doses) and CIS accelerated GE of a solid meal by decreasing the lag phase and increasing the rate of GE, whereas ERY only increased the rate of GE. The data suggest that ABT-229 is 7- to 40-fold more potent than ERY in accelerating GE.

L19 ANSWER 107 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2000429759 MEDLINE
DOCUMENT NUMBER: 20404085 PubMed ID: 10945850
TITLE: Dose-dependent effects of recombinant human interleukin-11 on contractile properties in rabbit 2,4,6-trinitrobenzene sulfonic acid colitis.
AUTHOR: Depoortere I; Thijs T; van Assche G; Keith J C Jr; Peeters T L

CORPORATE SOURCE: Centre for Gastroenterological Research, Department of Pathophysiology, University of Leuven, Belgium.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Sep) 294 (3) 983-90.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000922
Last Updated on STN: 20000922
Entered Medline: 20000912

AB We studied the effect of recombinant human interleukin-11 (rhIL-11), a cytokine with protective effects against injury to the intestinal mucosa, on inflammatory changes in the muscle layers of the gut, in rabbits with colitis. A single dose of rhIL-11 (4, 40, or 720 microg/kg) was given 1 h before colitis was induced with 135 mg/kg 2, 4,6-trinitrobenzene sulfonic acid (TNBS), followed by a continuous s. c. administration of 4, 40, or 720 microg/kg. day rhIL-11 or saline for 5 days. Colitis affected mucosal architecture, general mechanical properties (passive tension increased with 12.3 g/mm(2), optimal stretch decreased with 26%), and collagen content (decreased from 366 +/- 25 to 237 +/- 13 microg/mg of protein). Changes in passive tension and collagen content were normalized by the highest and lowest dose of rhIL-11, respectively, but neither dose could normalize the optimal stretch. Colitis also decreased maximal contractile tension in response to acetylcholine (ACh), motilin, substance P (SP), K(+), and prostaglandin E(2) but this was normalized with 40 microg/kg. day (motilin, SP) and 720 microg/kg. day (ACh, K(+)) rhIL-11 but not for prostaglandin E(2). For motilin and SP, receptor density was decreased in colitis and normalized in treated rabbits. Colitis also increased the contractile potency toward ACh, an effect already reversed by rhIL-11, 4 microg/kg. day. In conclusion, rhIL-11 partially normalizes disturbed tension generation in experimental colitis. The use of this cytokine in the treatment of irritable bowel disease may contribute to the restoration of motor dysfunction.

L19 ANSWER 108 OF 391 MEDLINE on STN DUPLICATE 46
ACCESSION NUMBER: 2000469492 MEDLINE
DOCUMENT NUMBER: 20344487 PubMed ID: 10886053
TITLE: Motilides accelerate regional gastrointestinal transit in the dog.
AUTHOR: Chiba T; Thomforde G M; Kost L J; Allen R G; Phillips S F
CORPORATE SOURCE: Division of Gastroenterology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (2000 Jul) 14 (7) 955-60.
Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001005

AB BACKGROUND: Motilides have prokinetic effects on the upper gut during fasting, increasing the strength of antral contractions and stimulating gastroduodenal phase 3 sequences. Effects on the distal gut, and postprandially, are less well documented. AIM: To evaluate dose-response effects of motilin and erythromycin on gastric emptying, small bowel and colonic transit in the dog using a validated scintigraphic technique. METHODS: For gastric emptying and small bowel transit, 99mTc labelled beads were added to a meal of dog chow (450 kcal). Regional colonic transit was measured by 111In labelled beads placed in a capsule which

dissolved and released radiation into the proximal colon. Scintiscans were taken at regular intervals and indices of whole-gut transit were calculated. Drugs were given by slow intravenous administration. RESULTS: In the doses used, motilin accelerated regional colonic transit but did not hasten gastric emptying or small bowel transit. Single or repeated doses of motilin had similar effects on colonic transit. Erythromycin accelerated gastric emptying, small bowel transit and regional colonic transit. CONCLUSIONS: **Motilin receptors** are apparently present in the canine small bowel and colon. Postprandially, motilides accelerate transit in the distal gut.

L19 ANSWER 109 OF 391 MEDLINE on STN
ACCESSION NUMBER: 2000234134 MEDLINE
DOCUMENT NUMBER: 20234134 PubMed ID: 10771639
TITLE: Orphan receptors: a fruitful resource for drug discovery.
AUTHOR: Sakurai T
CORPORATE SOURCE: Institure of Basic Medical Science, University of Tsukuba, Japan.. stakeshi@md.tsukuba.ac.jp
SOURCE: TANPAKUSHITSU KAKUSAN KOSO. PROTEIN, NUCLEIC ACID, ENZYME, (2000 Apr) 45 (6 Suppl) 821-6. Ref: 17
Journal code: 0413762. ISSN: 0039-9450.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000802

L19 ANSWER 110 OF 391 MEDLINE on STN DUPLICATE 47
ACCESSION NUMBER: 2001137161 MEDLINE
DOCUMENT NUMBER: 21005377 PubMed ID: 11143565
TITLE: Development and screening of a polyketide virtual library for drug leads against a motilide pharmacophore.
AUTHOR: Siani M A; Skillman A G; Carreras C W; Ashley G; Kuntz I D; Santi D V
CORPORATE SOURCE: Kosan Biosciences, 3832 Bay Center Place, Hayward, CA, USA.. siani@kosan.com
SOURCE: JOURNAL OF MOLECULAR GRAPHICS AND MODELLING, (2000 Aug-Oct) 18 (4-5) 497-511, 539-40.
Journal code: 9716237. ISSN: 1093-3263.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

AB A virtual library of macrocyclic polyketide molecules was generated and screened to identify novel, conformationally constrained potential **motilin receptor** agonists ("motilides"). A motilide pharmacophore model was generated from the potent 6,9-enol ether erythromycin and known derivatives from the literature. The pharmacophore for each molecular conformation was a point in a distance-volume space based on presentation of the putative binding moieties. Two methods, one fragment based method and the other reaction based, were explored for constructing the polyketide virtual library. First, a virtual library was assembled from monomeric fragments using the CHORTLES language. Second, the virtual library was assembled by the in silico application of all possible polyketide synthase enzyme reactions to generate the product library. Each library was converted to low-energy 3D conformations by

distance geometry and standard minimization methods. The distance-volume metric was calculated for low-energy conformations of the members of the virtual polyketide library and screened against the enol ether pharmacophore. The goal was to identify novel macrocycles that satisfy the pharmacophore. We identified three conformationally constrained, novel polyketide series that have low-energy conformations satisfying the distance-volume constraints of the motilide pharmacophore.

L19 ANSWER 111 OF 391 MEDLINE on STN DUPLICATE 48
ACCESSION NUMBER: 2000478910 MEDLINE
DOCUMENT NUMBER: 20484173 PubMed ID: 11027493
TITLE: Purification and identification of neuromedin U as an endogenous ligand for an orphan receptor GPR66 (FM3).
AUTHOR: Kojima M; Haruno R; Nakazato M; Date Y; Murakami N; Hanada R; Matsuo H; Kangawa K
CORPORATE SOURCE: Department of Biochemistry, National Cardiovascular Center Research Institute, Fujishirodai 5-7-1, Suita, Osaka, 565-8565, Japan.. mkoijima@ri.ncvc.go.jp
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Sep 24) 276 (2) 435-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001027
AB GPR66 is an orphan G-protein-coupled receptor (GPCR) whose structure is similar to the ghrelin and **motilin receptors.** We have tried to purify a natural ligand for GPR66 in rat tissues and identified a 23-amino-acid peptide as the endogenous ligand. Sequence analysis revealed the peptide as neuromedin U (NMU), a smooth-muscle-contracting peptide that was first purified from porcine spinal cord by our group. NMU binds to GPR66-expressing cells with high specificity to induce intracellular calcium mobilization. When NMU was injected intracerebroventricularly (ICV) into rats, it potently suppressed food intake. In contrast, ICV injection of NMU-antibody increased food intake. These results suggest that NMU is a potent endogenous anorexic peptide. Copyright 2000 Academic Press.

L19 ANSWER 112 OF 391 MEDLINE on STN DUPLICATE 49
ACCESSION NUMBER: 2001034556 MEDLINE
DOCUMENT NUMBER: 20414329 PubMed ID: 10959771
TITLE: Gastrointestinal functional bowel disorders: new therapies.
AUTHOR: Chovet M
CORPORATE SOURCE: Institut de Recherche Jouveinal/Parke-Davis, Fresnes, France.. maria.chovet@wl.com
SOURCE: CURRENT OPINION IN CHEMICAL BIOLOGY, (2000 Aug) 4 (4) 428-32. Ref: 51
Journal code: 9811312. ISSN: 1367-5931.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001130
AB Present therapies for functional gastrointestinal disorders are symptomatic and mainly treat altered bowel habits. New therapies are focused on nerve-gut communication dysfunction: 5-HT3 antagonists and

5-HT4 agonists have demonstrated activity in clinical trials. Promising targets for upper gut dysmotility drugs are motilin and cholecystokinin A receptors. Tachykinins, calcitonin gene-related peptide or glutamate antagonists are the most relevant candidates for visceral pain.

L19 ANSWER 113 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:274187 SCISEARCH
THE GENUINE ARTICLE: 300BZ
TITLE: In vitro effects of erythromycin, lidocaine, and metoclopramide on smooth muscle from the pyloric antrum, proximal portion of the duodenum, and middle portion of the jejunum of horses
AUTHOR: Nieto J E (Reprint); Rakestraw P C; Snyder J R; Vatistas N J
CORPORATE SOURCE: UNIV CALIF DAVIS, SCH VET MED, DEPT VET SURG & RADIOL SCI, COMPARAT GASTROENTEROL LAB, DAVIS, CA 95616 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF VETERINARY RESEARCH, (APR 2000) Vol. 61, No. 4, pp. 413-419.
Publisher: AMER VETERINARY MEDICAL ASSOC, 1931 N MEACHAM RD SUITE 100, SCHAUMBURG, IL 60173-4360.
ISSN: 0002-9645.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: AGRI
LANGUAGE: English
REFERENCE COUNT: 52

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective-To evaluate effects of erythromycin, lidocaine, and metoclopramide on smooth muscle of the pyloric antrum (PA), proximal portion of the duodenum (PD), and middle portion of the jejunum (MJ) of horses.

Sample Population-Strips of smooth muscle from 7 horses.

Procedure-Isolated muscle strips were suspended in a bath and attached to isometric force transducers. Once stable spontaneous contractions were observed, agents were added. Isometric stress responses were compared with the amplitude of spontaneous contractions.

Results-A single dose of erythromycin to the PA increased contractile amplitude (CA) for the longitudinal smooth muscle (mean +/- SEM, 76 +/- 16 g/cm(2)) but decreased CA for circular smooth muscle (-79 +/- 23 g/cm(2)). The inhibitory effect was decreased by tetrodotoxin, N-G-nitro-L-arginine methyl ester, and a vasoactive intestinal peptide antagonist. Erythromycin increased CA for the MJ, which was maximal at 10(-4)M (171 +/- 36 g/cm(2)). Lidocaine increased CA for the PD, which was maximal at 10(-4)M (60 +/- 5 g/cm(2)). Metoclopramide increased the CA, which was maximal at 10(-4)M for the PA (75 +/- 26 g/cm(2)), PD (279 +/- 33 g/cm(2)), and MJ (456 +/- 59 g/cm(2)).

Conclusions-Regional differences in responses to erythromycin, lidocaine, and metoclopramide were evident in the gastrointestinal tract of horses. Metoclopramide increased CA in all tissues used, whereas erythromycin inhibited CA in circular smooth muscle but stimulated CA in longitudinal smooth muscle from the PA. Inhibition is caused by stimulation of inhibitory nerves and is mediated, in part, by nitric oxide and vasoactive intestinal peptide.

L19 ANSWER 114 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:229228 CAPLUS
DOCUMENT NUMBER: 133:202847
TITLE: Erythromycin improves glycemic control in patients with Type II diabetes mellitus
AUTHOR(S): Ueno, N.; Inui, A.; Asakawa, A.; Takao, F.; Tani, S.; Komatsu, Y.; Itoh, Z.; Kasuga, M.
CORPORATE SOURCE: Second Department of Internal Medicine, Kobe University School of Medicine, Kobe, Japan
SOURCE: Diabetologia (2000), 43(4), 411-415
CODEN: DBTGAJ; ISSN: 0012-186X

PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Erythromycin mimics the effect of the gastrointestinal hormone motilin by binding to its receptor and acting as a motilin agonist. We recently found that motilin stimulates insulin secretion at lower doses than doses required to stimulate gastric contractile activity. We studied the effects of erythromycin on insulin secretion and glycemic control in patients with diabetes mellitus. Inpatients (n = 34) with Type II (non-insulin-dependent) diabetes mellitus were randomly assigned to receive either erythromycin (400 mg orally three times a day, n = 19) or a placebo (n = 15) for 1 wk (first study). Another 34 outpatients with Type II diabetes were also treated with erythromycin (200 mg orally three times a day, n = 17) or a placebo (n = 17) for 4 wk (second study). Finally, nine inpatients with Type II diabetes and eight normal control subjects received i.v. erythromycin (10 mg · kg-1 · h-1) or saline infusion and insulin secretion was examined (third study). Erythromycin lowered fasting blood glucose and fructosamine concns. ($p < 0.01$) and increased basal as well as glucose-stimulated insulin secretion ($p < 0.05$-0.01) (first study). Low doses of erythromycin treatment for 4 wk also significantly improved glycemic control in Type II diabetic patients (second study). Erythromycin infusion significantly increased plasma insulin and decreased glucose concns. in Type II diabetic and control subjects and greatly potentiated glucose-induced insulin secretion in the latter (third study). These results indicate that erythromycin given orally has an antidiabetogenic effect and therefore erythromycin derivs. that lack the antibacterial activity could have a therapeutic value in Type II diabetic patients.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 115 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 50

ACCESSION NUMBER: 2001:130255 BIOSIS
DOCUMENT NUMBER: PREV200100130255
TITLE: Administration of erythromycin dose not stimulate food intake in fasted chickens.
AUTHOR(S): Ando, Ryuichi [Reprint author]; Bungo, Takashi; Furuse, Mitsuhiro
CORPORATE SOURCE: Laboratory of Advanced Animal and Marine Bioresources, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, Fukuoka, 812-8581, Japan
SOURCE: Japanese Poultry Science, (November, 2000) Vol. 37, No. 6, pp. 372-378. print.
CODEN: NKKGAB. ISSN: 0029-0254.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Mar 2001
Last Updated on STN: 15 Feb 2002

AB Several neural peptides are known to stimulate feeding behavior in mammalian species. Among them, administration of motilin has been found to stimulate feeding behavior in rats and mice. However, central administration of mammalian motilin did not stimulate food intake of the neonatal chick in the previous study. Erythromycin acts as a smooth muscle **motilin receptor** agonist in mammals, but its effect on feeding behavior has not been investigated. The aim of this study was to elucidate whether administration of nonpeptidergic motilin agonist erythromycin stimulates feeding of fasted neonatal chicks. We administered erythromycin through intraperitoneal and oral routes, since it acts on the gut. No significant effects on food intake were obtained after intraperitoneal and oral administration of erythromycin. We also used the growing (4-week-old) chicken for oral administration of erythromycin, but no significant effect on food intake was obtained. These data suggested that erythromycin did not stimulate feeding in fasted chicks.

L19 ANSWER 116 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:263251 SCISEARCH
THE GENUINE ARTICLE: 298TB
TITLE: Prokinetic effects of erythromycin after antimotion sickness drugs
AUTHOR: Stewart J J (Reprint); Wood M J; Parish R C; Wood C D
CORPORATE SOURCE: LOUISIANA STATE UNIV, HLTH SCI CTR, DEPT PEDIAT, POB 33932, SHREVEPORT, LA 71130 (Reprint); LOUISIANA STATE UNIV, HLTH SCI CTR, DEPT PHARMACOL, SHREVEPORT, LA 71130; LOUISIANA STATE UNIV, HLTH SCI CTR, DEPT RADIOL, SHREVEPORT, LA 71130; LOUISIANNA UNIV, COLL PHARM, DEPT CLIN PHARM, MONROE, LA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF CLINICAL PHARMACOLOGY, (APR 2000) Vol. 40, No. 4, pp. 347-353.
Publisher: SAGE PUBLICATIONS INC, 2455 TELLER RD, THOUSAND OAKS, CA 91320.
ISSN: 0091-2700.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 28

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Motion sickness and the antimotion sickness drugs scopolamine (SCP) and promethazine (PMZ) inhibit gastric emptying (GE). This study was conducted to determine if erythromycin would exert its well-known prokinetic effects in normal and motion-sick subjects given antimotion sickness drugs. Fifteen fasted volunteers (11 males, 4 females) participated in the study. In control tests, 8 subjects were given intramuscular (IM) saline (SAL, 0.5 ml), SCP (0.1 mg), or PMZ (25 mg). GE of liquid (300 ml) containing 1 mCi of Tc 99m diethylenetriaminepentaacetic acid (DTPA) was measured by sequential gastric scintigraphy 30 minutes after IM treatments. In other tests, GE was measured in 8 subjects after each IM treatment, followed 10 minutes later by 200 mg of erythromycin ethylsuccinate (ESS) suspension given orally In a third group of tests, 7 subjects received an IM treatment oral EES 10 minutes later, and were then brought to an advanced level of motion sickness short of vomiting. To induce motion sickness, blindfolded subjects made timed head movements while seated in a rotating chair. GE was measured immediately after rotation. GE half-life, rate constant, area under the curve (AUC), and lag time were calculated using conventional mathematical methods for analyzing exponential rate processes. GE parameters calculated for normal and motion-sick subjects given antimotion sickness drugs and EES were compared with those from subjects given IM treatments (control) only. In normal subjects, EES significantly ($p < 0.05$) increased the GE rate constant for all IM treatments and reduced the AUC for SAL, SCP and PMZ by 49% ($p < 0.05$), 44% ($p < 0.05$), and 69% ($p < 0.01$), respectively In motion-sick subjects, lag time was significantly ($p < 0.05$) increased, and the rate constant and AUC values were unchanged from control for all IM treatments. The authors conclude that oral EES reverses the gastrostatic actions of the antimotion sickness drugs but does not affect the inhibition of gastric emptying associated with motion sickness. The results suggest that motion sickness and antimotion sickness drugs reduce GE through different mechanisms. Journal of Clinical Pharmacology, 2000;40:347-353 (C)2000 the American College of Clinical Pharmacology.

L19 ANSWER 117 OF 391 MEDLINE on STN DUPLICATE 51
ACCESSION NUMBER: 2000195252 MEDLINE
DOCUMENT NUMBER: 20195252 PubMed ID: 10733114
TITLE: Prokinetic effect of erythromycin after colorectal surgery: randomized, placebo-controlled, double-blind study.
AUTHOR: Smith A J; Nissan A; Lanouette N M; Shi W; Guillem J G; Wong W D; Thaler H; Cohen A M
CORPORATE SOURCE: Colorectal Service, Memorial Sloan-Kettering Cancer Center,

New York, New York, USA.
SOURCE: DISEASES OF THE COLON AND RECTUM, (2000 Mar) 43 (3) 333-7.
Journal code: 0372764. ISSN: 0012-3706.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000331

AB PURPOSE: Nausea and vomiting three to seven days after an elective operation on the colon and rectum remain a persistent clinical problem. Erythromycin, a safe, inexpensive drug that stimulates intestinal **motilin receptors**, has previously been shown to accelerate gastric emptying significantly after upper gastrointestinal surgery. We aimed to evaluate the effect of postoperative intravenous erythromycin on postoperative ileus in patients undergoing elective surgery for primary colorectal cancer. METHODS: Between May 1998 and April 1999, 150 patients undergoing primary resection of colon or rectal cancer were enrolled in this prospective, randomized, placebo-controlled trial. One hundred thirty-four patients completed the study. Patients were excluded if they had extensive metastatic disease, were taking medications known to interact with erythromycin, or if they required an ileostomy. Patients received either 200 mg of intravenous erythromycin or placebo every six hours. Clinical endpoints were recorded and continuous end-points are presented as mean +/- standard deviation. RESULTS: There were no significant complications related to erythromycin. The erythromycin (n = 65) and placebo (n = 69) groups were comparable regarding demographic and operative factors. The erythromycin group had a slightly shorter length of time to passage of flatus (4.1 +/- 1.3 vs. 4.4 +/- 1.1 days; P = 0.03). There was no significant difference between erythromycin and placebo in time to first solid food (5.6 +/- 1.9 vs. 5.4 +/- 1.8 days), time to first bowel movement (5.2 +/- 1.9 vs. 5.4 +/- 1.3 days), or time to discharge from hospital (7.5 +/- 2.0 vs. 7.6 +/- 2.8 days). There was no difference in the rate of clinically significant nausea (26 vs. 26 percent; P = 0.99), vomiting (17 vs. 16 percent; P = 0.88), or nasogastric tube placement (9 vs. 7 percent; P = 0.68). CONCLUSIONS: Erythromycin does not seem to alter clinically important outcomes related to postoperative ileus in patients undergoing resection for colorectal cancer.

L19 ANSWER 118 OF 391 MEDLINE on STN DUPLICATE 52
ACCESSION NUMBER: 2000230048 MEDLINE
DOCUMENT NUMBER: 20230048 PubMed ID: 10764957
TITLE: Neural and muscular receptors for motilin in the rabbit colon.
AUTHOR: Miller P; Trudel L; St-Pierre S; Takanashi H; Poitras P
CORPORATE SOURCE: Centre Hospitalier de l'Universite de Montreal, Hopital Saint-Luc, Centre de Recherche, 264 Blvd. Rene-Levesque Est, Montreal, Quebec, Canada.
SOURCE: PEPTIDES, (2000 Feb) 21 (2) 283-7.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000608

AB **Motilin receptors** were classically recognized in the gastroduodenal area, where they help to regulate interdigestive motility.

More recently, **motilin receptors** were identified in the colon where their biologic significance remains unclear. We aimed here to characterize the **motilin receptors** of the rabbit colon. Distal colon and duodenum were obtained from sacrificed rabbits. Tissues homogenized by Polytron were submitted to differential centrifugation to obtain neural synaptosomes or smooth muscle plasma membranes enriched solutions. Motilin binding to these membranes was determined by the displacement of (125)I MOT by the native peptide MOT 1-22, or by peptide analogues MOT 1-12 [CH(2)NH](10-11) or GM-109 and by erythromycin derivative GM-611. Motilin binding capacity was maximum in colon nerves (49.5 +/- 6.5 fmol/mg protein vs. 19.9 +/- 2.5 in colon muscles or 9.4 +/- 2.8 and 6.6 +/- 1.2 in duodenal muscles and antral nerves respectively); all tissues expressed similar affinity for MOT 1-22, and the motilin agonist GM-611 bound equally to neural or muscle tissues from the rabbit colon; the synthetic antagonist MOT 1-12 [CH(2)NH](10-11) showed greater affinity for colon nerves than for colon muscles (plC50: 7.23 +/- 0.07 vs. 6.75 +/- 0.03). Similar results were obtained with the peptide antagonist GM-109; receptor affinity toward MOT 1-12 [CH(2)NH(10-11)] was always five times superior in neural tissues, whether they came from the colon or the antrum, than in muscle tissues, whether they were obtained from colon or from duodenum. **Motilin receptors** are found in very high concentration in nerves and in muscles from rabbit colon; specific **motilin receptor** subtypes are identified in nerves (N) and muscles (M) of the rabbit colon; N and M receptor subtypes seem independent of the organ location.

L19 ANSWER 119 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001265119 EMBASE

TITLE: Discovery of the first non-peptide antagonist of the **motilin receptor.**

AUTHOR: Beavers M.P.; Gunnet J.W.; Hageman W.; Miller W.; Moore J.B.; Zhou L.; Chen R.H.K.; Xiang A.; Urbanski M.; Combs D.W.; Mayo K.H.; Demarest K.T.

CORPORATE SOURCE: M.P. Beavers, R.W. Johnson Pharmaceut. Res. Inst., 1000 Rt. 202, Raritan, NJ 08869, United States

SOURCE: Drug Design and Discovery, (2000) 17/3 (243-251).
Refs: 23
ISSN: 1055-9612 CODEN: DDDIEV

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
048 Gastroenterology
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A first-in-class non-peptide antagonist of the **motilin receptor** was identified through electronic screening of our corporate database against a 3D pharmacophore. The pharmacophore was developed from the motilin 22 residue endogenous peptide using NMR structural data, principles of peptide folding, and peptide structure activity relationships. The NMR data supported helical content within the peptide, and both the hydrophobic staple and N-capping box motifs were identified in the motilin sequence. The conformational features of these motifs were imposed on the peptide structure, providing a constrained conformer as a starting point for database searching. A trisubstituted cyclopentene lead was identified directly from the electronic search. Compounds in this series inhibit the binding of (125)I-motilin to human antral smooth muscle membrane and antagonize motilin-induced intracellular calcium mobilization in cells expressing the human **motilin receptor.** A potent compound developed through optimization, RWJ 68023, is active in binding and cell-based functional assays and is also effective in inhibiting motilin-induced contractility in segments of rabbit duodenum. This orally active compound is currently undergoing

clinical evaluation for the treatment of gastrointestinal disorders associated with altered motility.

L19 ANSWER 120 OF 391 MEDLINE on STN DUPLICATE 53
ACCESSION NUMBER: 2001233944 MEDLINE
DOCUMENT NUMBER: 21138921 PubMed ID: 11245302
TITLE: Characterization of the **motilin receptor** , a member of a new receptor family.
AUTHOR: Miller L J; Coulie B
CORPORATE SOURCE: Center for Basic Research in Digestive Diseases, Mayo Clinic and Foundation, Rochester, MN 55905, USA.. miller@mayo.edu
SOURCE: DIGESTIVE AND LIVER DISEASE, (2000 Dec) 32 Suppl 3 S223-4. Journal code: 100958385. ISSN: 1590-8658.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20021030
Entered Medline: 20010503

L19 ANSWER 121 OF 391 MEDLINE on STN DUPLICATE 54
ACCESSION NUMBER: 2000420324 MEDLINE
DOCUMENT NUMBER: 20256886 PubMed ID: 10794824
TITLE: EM574, an erythromycin derivative, improves delayed gastric emptying of semi-solid meals in conscious dogs.
COMMENT: Erratum in: Eur J Pharmacol 2000 Sep 22;404(3):397
AUTHOR: Sato F; Marui S; Inatomi N; Itoh Z; Omura S
CORPORATE SOURCE: Pharmacology Laboratories II, Takeda Chemical Industries, Ltd., 2-17-85, Juso-Honmachi, Yodogawa-ku, Osaka, Japan.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2000 Apr 28) 395 (2) 165-72. Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20010611
Entered Medline: 20000906

AB The gastroprokinetic effects of de(N-methyl)-N-isopropyl-8, 9-anhydroerythromycin A 6,9-hemiacetal (EM574), a non-peptide **motilin receptor** agonist, were investigated in conscious dogs in a normal state and with experimentally-induced gastroparesis. Gastric emptying of semi-solid meals was assessed indirectly from acetaminophen absorption with simultaneous recording of gastric antral motility. In the normal state, post-prandial intraduodenal administration of EM574 (0.03 mg/kg) [corrected] stimulated antral motility and significantly enhanced gastric emptying as potently as did intravenous porcine motilin (0.003 mg/kg/h). Intraduodenal cisapride at 1 mg/kg denal cisapride at 1 mg/kg elicited antral contractions and tended to accelerate gastric emptying but at 3 mg/kg, gastric emptying was not enhanced despite a further increase in the motor index. In dogs with gastroparesis induced by intraduodenal oleic acid or intravenous dopamine, EM574 (0.03 mg/kg) increased antral motility and reversed the delayed gastric emptying completely. Cisapride (1 mg/kg) partially ameliorated the impaired emptying under these conditions. In atropinized dogs, no acceleration of gastric emptying by EM574 was observed. These results indicate that EM574 potently accelerates gastric emptying of caloric meals in dogs in a normal state and with experimentally-induced gastroparesis, and also suggest that the effect is mediated through stimulation of a cholinergic neural pathway.

L19 ANSWER 122 OF 391 MEDLINE on STN DUPLICATE 55
ACCESSION NUMBER: 2000092336 MEDLINE
DOCUMENT NUMBER: 20092336 PubMed ID: 10628755
TITLE: Ligand activation domain of human orphan growth hormone (GH) secretagogue receptor (GHS-R) conserved from Pufferfish to humans.
AUTHOR: Palyha O C; Feighner S D; Tan C P; McKee K K; Hreniuk D L; Gao Y D; Schleim K D; Yang L; Morriello G J; Nargund R; Patchett A A; Howard A D; Smith R G
CORPORATE SOURCE: Department of Biochemistry and Physiology, Merck Research Laboratories, Rahway, New Jersey 07065, USA.
SOURCE: MOLECULAR ENDOCRINOLOGY, (2000 Jan) 14 (1) 160-9.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB Synthetic ligands have been identified that reset and amplify the cycle of pulsatile GH secretion by interacting with the orphan GH-secretagogue receptor (GHS-R). The GHS-R is rhodopsin like, but does not obviously belong to any of the established G protein-coupled receptor (GPCR) subfamilies. We recently characterized the closely related orphan family member, GPR38, as the **motilin receptor.** A common property of both receptors is that they amplify and sustain pulsatile biological responses in the continued presence of their respective ligands. To efficiently identify additional members of this new GPCR family, we explored a vertebrate species having a compact genome, that was evolutionary distant from human, but where functionally important genes were likely to be conserved. Accordingly, three distinct full-length clones, encoding proteins of significant identity to the human GHS-R, were isolated from the Pufferfish (Spheroides nephelus). Southern analyses showed that the three cloned Pufferfish genes are highly conserved across species. The gene with closest identity (58%) was activated by three synthetic ligands that were chosen for their very high selectivity on the GHS-R as illustrated by their specificity in activating the wild-type human GHS-R but not the E124Q mutant. These results indicate that the ligand activation domain of the GHS-R has been evolutionary conserved from Pufferfish to human (400 million years), supporting the notion that the GHS-R and its natural ligand play a fundamentally important role in biology. Furthermore, they illustrate the power of exploiting the compact Pufferfish genome for simplifying the isolation of endocrinologically important receptor families.

L19 ANSWER 123 OF 391 MEDLINE on STN DUPLICATE 56
ACCESSION NUMBER: 2000219504 MEDLINE
DOCUMENT NUMBER: 20219504 PubMed ID: 10754449
TITLE: In vitro pharmacological profile of SK-896, a new human motilin analogue.
AUTHOR: Tsukamoto K; Kuboyama N; Yamano M; Nakazawa T; Suzuki T
CORPORATE SOURCE: Pharmaceutical Laboratory, Sanwa Kagaku Kenkyusho Co., Ltd., Mie, Japan.. k_tsukamoto@mb4.skk-net.com
SOURCE: PHARMACOLOGY, (2000 Apr) 60 (3) 128-35.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20000720

Entered Medline: 20000712

AB SK-896 ([Leu(13)]motilin-Hse) is a new human motilin analogue synthesized by Escherichia coli using a biotechnological method. We investigated the binding of SK-896 to **motilin receptors** and the contractile effect of SK-896 on smooth muscle preparations isolated from the gastrointestinal tract and various regional organs in order to clarify its in vitro pharmacological profile. SK-896 inhibited the binding of (125)I-human motilin to rabbit gastroduodenal **motilin receptors** with the same potency as unlabeled human motilin. The IC(50) values of SK-896 and human motilin were 3.5 +/- 1.5 and 3.1 +/- 1.8 nmol/l, respectively. The K(d) of human motilin was 3.0 +/- 1.5 nmol/l, and the Ki of SK-896 was 3.4 +/- 1.5 nmol/l. SK-896 induced contraction of smooth muscle preparations isolated from rabbit duodenum in a concentration-dependent manner. However, there was no effect of SK-896 on duodenal preparations isolated from the dog and the rat. SK-896 thus exhibited species specificity in its contractile effect. We next investigated the effect of SK-896 on various smooth muscle preparations isolated from rabbit gastrointestinal tract, trachea, bladder, gallbladder, uterus, vas deferens and artery. Results showed that SK-896 induced contraction of smooth muscle preparations isolated from gastrointestinal tract, with potencies in the order duodenum > gastric pylorus = jejunum = descending colon > ascending colon >/= ileum. However, there was no effect of SK-896 on smooth muscle preparations from gastric fundus and other regional organs. SK-896 thus exhibited regional specificity in its contractile effect. Moreover, the effects of SK-896 on smooth muscle preparations from rabbit duodenum were the same as those of human motilin, and were not inhibited by pretreatment with tetrodotoxin and atropine but were inhibited by verapamil. These findings indicate that SK-896 has the same pharmacological profile as human motilin. They suggest that SK-896 acts on gastrointestinal smooth muscle isolated from rabbit directly and specifically.

L19 ANSWER 124 OF 391 MEDLINE on STN DUPLICATE 57

ACCESSION NUMBER: 2000086840 MEDLINE
DOCUMENT NUMBER: 20086840 PubMed ID: 10620004
TITLE: Effects of erythromycin on human colonic circular muscle in idiopathic chronic constipation.
AUTHOR: Chieppa D M; Mansi G; Rinaldi R; Serio M; Nacci C; Montagnani M; Potenza M A; De Salvia M A; Mitolo C I; Rinaldi M; Altomare D F
CORPORATE SOURCE: Medical School, University of Bari, Italy.. chieppa@farmacol.uniba.it
SOURCE: EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, (2000 Jan) 30 (1) 66-71.
Journal code: 0245331. ISSN: 0014-2972.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000210

AB BACKGROUND: Erythromycin has been shown to have profound prokinetic effects on the gastrointestinal tract of humans and animals, probably through its action on endogenous **motilin receptors.** The purpose of this study was to determine both the direct and indirect effects ('off contraction') of erythromycin and motilin on ex vivo circular muscle strips of the distal colon from patients with or without idiopathic chronic constipation (ICC). MATERIALS AND METHODS: Cumulative concentrations of erythromycin (1-20 microM) and motilin (0.05-1 microM) were tested in both control and ICC preparations in order to evaluate the direct drugs effect. A range doses of both erythromycin (0.5-10 microM) and motilin (0.05-0.5 microM) were tested on their ability to affect the

off-contraction that follows the typical inhibitory response evoked by low frequencies of Electrical Field Stimulation (EFS) (1-5 Hz, 20 V, 1 msec pulse trains lasting 1 min). RESULTS: The direct effect of both erythromycin and motilin was a slight increase (less than 10% of the maximal ACh-induced contraction) in the basal tension, with no dose-response relationship. The off-contraction, evoked by EFS, was not affected by drugs pretreament in control preparations. Conversely, in ICC preparations both drugs significantly increased the off-contraction (about 30%). CONCLUSIONS: Erythromycin causes mainly an indirect contractile effect in circular muscle strips from ICC patients. This effect may be related to the activation of inhibitory neuronal **motilin receptors.** This activation might potentiate NANC relaxation, proportionally increasing the circumferential reflex contraction that follows the EFS-induced relaxation.

L19 ANSWER 125 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:534590 BIOSIS
DOCUMENT NUMBER: PREV200100534590
TITLE: Effects of intravenous erythromycin on gallbladder contractility in preterm neonates.
AUTHOR(S): Steinberg, I. [Reprint author]; Tesmer, K. [Reprint author]; Durand, M. [Reprint author]; Sinatra, F. R. [Reprint author]
CORPORATE SOURCE: Department of Pediatrics, University of Southern California Schools of Medicine and Pharmacy, Los Angeles, CA, USA
SOURCE: Journal of Investigative Medicine, (January, 2000) Vol. 48, No. 1, pp. 50A. print.
Meeting Info.: Meeting of the American Federation for Medical Research, Western Region. Carmel, California, USA. February 09-12, 2000.
ISSN: 1081-5589.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Nov 2001
Last Updated on STN: 23 Feb 2002

L19 ANSWER 126 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:482377 BIOSIS
DOCUMENT NUMBER: PREV200000482377
TITLE: Small intestinal manometric findings in a patient with total intestinal aganglionosis.
AUTHOR(S): Takahashi, Atsushi [Reprint author]; Tomomasa, Takeshi; Suzuki, Norio; Kuroiwa, Minoru; Ikeda, Hitoshi; Tabata, Masahiko; Kaneko, Hiroaki; Morikawa, Akihiro; Tsuchida, Yoshiaki
CORPORATE SOURCE: Surgery, Gunma Children's Medical Center, Hokkitsu, Japan
SOURCE: JPGN, (2000) Vol. 31, No. Supplement 2, pp. S35. print.
Meeting Info.: World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. Boston, Massachusetts, USA. August 05-09, 2000.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Nov 2000
Last Updated on STN: 10 Jan 2002

L19 ANSWER 127 OF 391 MEDLINE on STN DUPLICATE 58
ACCESSION NUMBER: 2000113225 MEDLINE
DOCUMENT NUMBER: 20113225 PubMed ID: 10644557
TITLE: **Motilin receptors** in the human antrum.
AUTHOR: Miller P; Roy A; St-Pierre S; Dagenais M; Lapointe R; Poitras P
CORPORATE SOURCE: Gastrointestinal Unit, Centre Hospitalier de l'Universite

de Montreal, Montreal, Quebec, Canada H2X 3J4.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. GASTROINTESTINAL AND LIVER PHYSIOLOGY, (2000 Jan) 278 (1) G18-23.
Journal code: 100901227. ISSN: 0193-1857.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000616

AB Motilin is an intestinal peptide that stimulates contraction of gut smooth muscle. The **motilin receptor** has not been cloned yet, but **motilin-receptor** agonists appear to be potent prokinetic agents for the treatment of dysmotility disorders. The aim of this study was to determine neural or muscular localization of **motilin receptors** in human upper gastrointestinal tract and to investigate their pharmacological characteristics. The binding of (125)I-labeled motilin to tissue membranes prepared from human stomach and duodenum was studied; rabbit tissues were used for comparison. Solutions enriched in neural synaptosomes or in smooth muscle plasma membranes were obtained. Various motilin analogs were used to displace the motilin radioligand from the various tissue membranes. The highest concentration of human **motilin receptors** was found in the antrum, predominantly in the neural preparation. Human **motilin receptors** were sensitive to the NH(2)-terminal portion of the motilin molecule, but comparison with rabbit showed that both species had specific affinities for various motilin analogs [i.e., Mot-(1-9), Mot-(1-12), Mot-(1-12) (CH(2)NH)(10-11), and erythromycin]. **Motilin receptors** obtained from synaptosomes or muscular plasma membranes of human antrum expressed different affinity for two **motilin-receptor** agonists, Mot-(1-12) and Mot-(1-12) (CH(2)NH)(10-11), suggesting that they correspond to specific receptor subtypes. We conclude that human **motilin receptors** are located predominantly in nerves of the antral wall, are functionally (and probably structurally) different from those found in other species such as the rabbit, and express specific functional (and probably structural) characteristics dependent on their localization on antral nerves or muscles, suggesting the existence of specific receptor subtypes, potentially of significant physiological or pharmacological relevance.

L19 ANSWER 128 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 59
ACCESSION NUMBER: 2000-105868 [09] WPIDS
DOC. NO. CPI: C2000-031800
TITLE: Novel receptor protein for screening compounds used in treating irritable bowel syndrome, constipation and other gastric conditions.
DERWENT CLASS: B04 D16
INVENTOR(S): FEIGHNER, S D; HOWARD, A D; MACNEIL, D; MCKEE, K; PATCHETT, A A; PONG, S; SMITH, R G; TAN, C
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9964436	A1	19991216	(200009)*	EN	35
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP US					
EP 1086117	A1	20010328	(200118)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
JP 2002517507 W		20020618	(200242)		42

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9964436	A1	WO 1999-US12773	19990608
EP 1086117	A1	EP 1999-928453	19990608
		WO 1999-US12773	19990608
JP 2002517507	W	WO 1999-US12773	19990608
		JP 2000-553444	19990608

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1086117	A1	Based on	WO 9964436
JP 2002517507	W	Based on	WO 9964436

PRIORITY APPLN. INFO: US 1998-89098P 19980612
AN 2000-105868 [09] WPIDS
AB WO 9964436 A UPAB: 20000218
NOVELTY - A **motilin receptor** (I) MTL-R1 (GPR 38) which is substantially free from receptor associated proteins, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of determining binding of a ligand (II) to (I) comprising:

(a) transfecting test cells with an expression vector encoding (I);

(b) exposing them to (II);

(c) measuring amount of binding of (II) to (I); and

(d) comparing this level to that of the amount of binding of (II) to control cells that have not been transfected with (I), a greater level of binding in the test cells compared determines that (II) is capable of binding (I).

ACTIVITY - Dermatological; antidiabetic; laxative; litholytic; antiinflammatory; antidiarrheic.

MECHANISM OF ACTION - Stimulator or inhibitor of **motilin receptor.**

USE - (I) is used to identify its agonists and antagonists which can be used for treating gastric motility disorders, functional defects, disorders secondary to neurological disorders e.g. scleroderma, paraneoplastic syndromes radiation induced dysmotility, diabetes, infections, stress-related motility disorders, psychgenic disorders, gastroparesis, gastro-esophageal reflux disease, constipation, chronic idiopathis pseudo obstruction, acute fecal impaction, postoperative ileus, gallstones, infantile collic, irritable bowel syndrome, non-ulcer dyspepsion, non-cardiac chest pain and diarrhea. They can also be used in the preparation for colonoscopy, endoscopy and duodenal intubation. Nucleic acid encoding (I) or its functional variants can be used as DNA probes to identify **motilin receptor** from other species.

ADVANTAGE - (I) enables the identification of safe and selective **motilin receptor** agonists.

Dwg.0/11

L19 ANSWER 129 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 60

ACCESSION NUMBER: 1999-312927 [26] WPIDS
DOC. NO. CPI: C1999-092367
TITLE: New cyclopentene derivatives useful in treating gastrointestinal disorders associated with antagonising the **motilin receptor**, including e.g. irritable bowel syndrome.
DERWENT CLASS: B02 B03
INVENTOR(S): BEAVERS, M P; CHEN, R H; MOORE, J B; XIANG, M; BEAVERS, M; CHEN, R; XIANG, M A
PATENT ASSIGNEE(S): (ORTH) ORTHO-MCNEIL PHARM INC; (ORTH) ORTHO-MCNEIL PHARM CORP; (JOHJ) JOHNSON & JOHNSON

COUNTRY COUNT: 85
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9921846	A1	19990506	(199926)*	EN	56
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9912024	A	19990517	(199939)		
US 5972939	A	19991026	(199952)		
EP 1027342	A1	20000816	(200040)	EN	
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI					
NO 2000002036	A	20000614	(200041)		
ZA 9809784	A	20000726	(200042)		57
BR 9813169	A	20000822	(200050)		
CZ 2000001447	A3	20000913	(200054)		
SK 2000000606	A3	20001107	(200102)		
CN 1278255	A	20001227	(200123)		
HU 2000004851	A2	20010528	(200140)		
KR 2001031569	A	20010416	(200163)		
AU 738370	B	20010913	(200164)		
JP 2001521030	W	20011106	(200203)		72
TW 466225	A	20011201	(200252)		
MX 2000004133	A1	20011201	(200282)		
NO 316118	B1	20031215	(200382)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9921846	A1		WO 1998-US22765	19981027
AU 9912024	A		AU 1999-12024	19981027
US 5972939	A	Provisional	US 1997-63669P	19971028
			US 1998-179135	19981026
EP 1027342	A1		EP 1998-955148	19981027
			WO 1998-US22765	19981027
NO 2000002036	A		WO 1998-US22765	19981027
			NO 2000-2036	20000418
ZA 9809784	A		ZA 1998-9784	19981027
BR 9813169	A		BR 1998-13169	19981027
			WO 1998-US22765	19981027
CZ 2000001447	A3		WO 1998-US22765	19981027
			CZ 2000-1447	19981027
SK 2000000606	A3		WO 1998-US22765	19981027
			SK 2000-606	19981027
CN 1278255	A		CN 1998-810629	19981027
HU 2000004851	A2		WO 1998-US22765	19981027
			HU 2000-4851	19981027
KR 2001031569	A		KR 2000-704615	20000428
AU 738370	B		AU 1999-12024	19981027
JP 2001521030	W		WO 1998-US22765	19981027
			JP 2000-517958	19981027
TW 466225	A		TW 1998-117818	19981210
MX 2000004133	A1		MX 2000-4133	20000427
NO 316118	B1		WO 1998-US22765	19981027
			NO 2000-2036	20000418

FILING DETAILS:

PATENT NO	KIND		PATENT NO

AU 9912024	A	Based on	WO 9921846
EP 1027342	A1	Based on	WO 9921846
BR 9813169	A	Based on	WO 9921846
CZ 2000001447	A3	Based on	WO 9921846
HU 2000004851	A2	Based on	WO 9921846
AU 738370	B	Previous Publ.	AU 9912024
		Based on	WO 9921846
JP 2001521030	W	Based on	WO 9921846
NO 316118	B1	Previous Publ.	NO 2000002036

PRIORITY APPLN. INFO: US 1997-63669P 19971028; US 1998-179135 19981026

AN 1999-312927 [26] WPIDS

AB WO 9921846 A UPAB: 20011203

NOVELTY - Novel cyclopentene derivatives are useful in treating gastrointestinal disorders associated with antagonising the motilin receptor.

DETAILED DESCRIPTION - Cyclopentene derivatives of formula (I) and their salts are new.

R1 = H, 1-5C alkyl (optionally substituted by one or more halo), amino(1-5C)alkyl, 1-5C alkylamino(1-5C)alkyl, di(1-5C alkyl)amino(1-5C)alkyl, RaRbN(1-5C alkyl), 1-5C alkylcarbonyl, 1-5C alkoxycarbonyl, aminocarbonyl, 1-9C alkyl amino carbonyl, cyclo(3-9C)alkylaminocarbonyl, pyridinylcarbonyl (optionally ring substituted by one or more halo or 1-5C alkyl), thiophene carbonyl (optionally ring substituted by one or more halo or 1-5C alkyl), optionally substituted phenyl, optionally substituted phenyl(1-5C)alkyl, optionally substituted phenoxycarbonyl, optionally substituted phenylcarbonyl, optionally substituted diphenylmethylcarbonyl, optionally substituted phenylaminocarbonyl, optionally substituted phenylthiocarbonyl or phenylaminothiocarbonyl (optionally ring substituted by one or more halo, 1-5C alkyl, trihalomethyl, 1-5C alkoxy, amino, CN, NO2, 1-5C alkylamino, di(1-5C alkyl) amino and more than one substituent may be taken together with the phenyl ring to form a fused bicyclic 7-10 membered heterocycle having 1 or 2 O, S or N or the substituents may be taken together to form a fused bicyclic 7-10 membered aromatic ring);

Ra, Rb = H or 1-5C alkyl; or

Ra+Rb = morpholine, piperazine, piperidine or piperidine N-substituted by 1-5C alkyl or phenyl(1-5C)alkyl;

R2 = H, 1-5C alkyl, 1-5C alkoxy, phenyl (optionally substituted by one or more halo or 1-5C alkyl), or phenyl(1-5C)alkyl (optionally ring substituted by one or more halo, 1-5C alkyl, 1-5C alkoxy or di(1-5C alkyl)amino);

R3 = H, 1-5C alkylcarbonyl (optionally substituted by one or more halo) or phenylcarbonyl (optionally ring substituted by one or more halo, 1-5C alkyl, 1-5C alkoxy, NH2, 12-5C alkylamino or di(1-5C alkyl)amino);

R4 = H, 1-5C alkylcarbonyl (optionally substituted by one or more halo), or phenylcarbonyl (optionally ring substituted by one or more halo, 1-5C alkyl, 1-5C alkoxy, amino, 1-5C alkylamino or di(1-5C alkyl)amino;

n = 0-3;

m = 1-5;

R5 = X(CH2)z(A)t;

q = 0-2;

t = 0-1;

X = O, CH2, S or NRc;

Rc = H, 1-5C alkyl, morpholino(1-5C)alkyl, piperidinyl(1-5C)alkyl, N-phenylmethylpiperidinyl or piperazinyl(1-5C)alkyl;

A = 1-5C alkoxycarbonyl, phenylcarbonyl or NR7R8;

R7, R8 = H, 1-5C alkyl or cyclo (1-9C) alkyl; or

R7+R8 = 5 or 6 membered heterocycle containing one or more O, N or S or their N-oxides;

R6 = H, halo, 1-5C alkoxy, 1-5C alkylamino or di(1-5C alkyl)amino.

provided that if q and t = 0, then X = OH, SH or NH2.

ACTIVITY - Gastrointestinal.

The compounds were evaluated for their ability to inhibit motilin and

erythromycin induced contractions in the rabbit duodenum smooth muscle. (Ia) exhibited 98% inhibition at 20 micro M.

MECHANISM OF ACTION - MECHANISM OF ACTION - **Motilin receptor** antagonist.

USE - (I) are useful for treating gastrointestinal disorders associated with the **motilin receptor** including irritable bowel syndrome, oesophageal reflux, and the gastrointestinal side effects of erythromycin. The compounds compete with erythromycin and motilin for the **motilin receptor.** In addition (I) are antagonists of the contractile smooth muscle response to those ligands. Dwg.0/0

L19 ANSWER 130 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 61

ACCESSION NUMBER: 1999-180967 [15] WPIDS
DOC. NO. CPI: C1999-052835
TITLE: New phenethylamine derivatives are **motilin receptor** antagonists - for treating e.g. Crohn's disease, pancreatitis, diabetes and obesity.
DERWENT CLASS: B04 B05
INVENTOR(S): KOTAKE, K; KOZONO, T; SATO, T; TAKANASHI, H
PATENT ASSIGNEE(S): (CHUS) CHUGAI SEIYAKU KK; (CHUS) CHUGAI PHARM CO LTD
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9909053	A1	19990225	(199915)*	JA	145
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9886490	A	19990308	(199929)		
JP 2000044595	A	20000215	(200019)		63
EP 1006122	A1	20000607	(200032)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1272114	A	20001101	(200112)		
US 6255285	B1	20010703	(200140)		
KR 2001022924	A	20010326	(200161)		
AU 741216	B	20011129	(200206)		
TW 460478	A	20011021	(200248)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9909053	A1	WO 1998-JP3627	19980814
AU 9886490	A	AU 1998-86490	19980814
JP 2000044595	A	JP 1998-229586	19980814
EP 1006122	A1	EP 1998-937826	19980814
		WO 1998-JP3627	19980814
CN 1272114	A	CN 1998-809657	19980814
US 6255285	B1	WO 1998-JP3627	19980814
		US 2000-485620	20000215
KR 2001022924	A	KR 2000-701529	20000215
AU 741216	B	AU 1998-86490	19980814
TW 460478	A	TW 1998-113211	19980811

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9886490	A	Based on	WO 9909053

EP 1006122 A1 Based on WO 9909053
US 6255285 B1 Based on WO 9909053
AU 741216 B Previous Publ. AU 9886490
Based on WO 9909053

PRIORITY APPLN. INFO: JP 1998-186802 19980528; JP 1997-255879 19970815
AN 1999-180967 [15] WPIDS
AB WO 9909053 A UPAB: 19990416
NOVELTY - Phenethylamine derivatives (I) are new.
DETAILED DESCRIPTION - Phenethylamine derivatives of formula (I) and their salts and hydrates are new. A = amino acid or N alpha -amino acid and A and NR2 form an amide bond; R1 = R6CO or optionally substituted 2-7C alkyl, 3-8C alkenyl or 3-8C alkynyl; R2 = H or 1-3C alkyl; R3 = COR7 or optionally substituted 1-5C alkyl, 2-5C alkenyl or 2-5C alkynyl; R4 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl or CR15R16R17; R5 = H or OR8; R6 = NR9R10, OR11, 3-7C cycloalkyl (optionally fused to a benzene or heterocyclic ring) or optionally substituted 1-6C alkyl, 2-7C alkenyl, 2-7C alkynyl, 6-12C aromatic ring or 3-12C optionally unsaturated heterocyclyl; R7 = H, 3-7C cycloalkyl, NR12R13, OR14 or optionally substituted 1-5C alkyl; R8 = H or 1-4C alkyl; R9, R10 = H or R11; R11 = 3-6C cycloalkyl (optionally fused to a benzene or heterocyclic ring) or optionally substituted 1-5C alkyl, 2-6C alkenyl, 2-6C alkynyl or 6-12C aromatic ring; R12, R13 = H, 1-4C alkyl, or 3-7C cycloalkyl; R14 = H, 1-6C alkyl or 3-7C cycloalkyl; R15 = H or Me; R16, R17 = 3-7C cycloalkyl or cycloalkenyl.
ACTIVITY - Antiinflammatory; Antiulcer; Antidiabetic; Anorectic.
MECHANISM OF ACTION - **Motilin receptor** antagonists. N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide (Ia) had an IC50 value for **motilin receptor** binding, using the method of Bormans et al., Reg. Peptides, 15 143(1986), of 1.9 nM.
USE - (I) are useful for the treatment of Crohn's disease, ulcerative colitis, pancreatitis, diabetes, obesity, intestinal motility disorders, nutritional absorption disorders, low bacterial activity, irritable bowel syndrome or gastritis.
Dwg.0/0

L19 ANSWER 131 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:290007 BIOSIS
DOCUMENT NUMBER: PREV200000290007
TITLE: Cyclopentene derivatives useful as antagonists of the **motilin receptor.**
AUTHOR(S): Chen, Robert H. [Inventor, Reprint author]; Xiang, Min [Inventor]; Moore, John B. [Inventor]; Beavers, Mary Pat [Inventor]
CORPORATE SOURCE: New Hope, PA, USA
ASSIGNEE: Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, USA
PATENT INFORMATION: US 5972939 October 26, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct. 26, 1999) Vol. 1227, No. 4. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002
AB The compounds of formula I are useful in treating gastrointestinal disorders associated with antagonizing the **motilin receptor** disorders. The compounds compete with erythromycin and motilin for the **motilin receptor.** In addition the compounds are antagonists of the contractile smooth muscle response to those ligands.

L19 ANSWER 132 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 1999-509364 [43] WPIDS
DOC. NO. CPI: C1999-149053
TITLE: New contracted ring derivatives of erythromycin A which do not have antibiotic activity and are useful in treatment of motility disorders.
DERWENT CLASS: B02
INVENTOR(S): EECKHOUT, C; JASSERAND, D; PREUSCHOFF, U
PATENT ASSIGNEE(S): (SOLV) SOLVAY PHARM GMBH; (KALI) KALI-CHEMIE PHARMA GMBH
COUNTRY COUNT: 40
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19805822	A1	19990819	(199943)*		8
EP 937734	A1	19990825	(199943)	GE	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
NO 9900675	A	19990816	(199943)		
CZ 9900458	A3	19990915	(199945)		
AU 9916438	A	19990826	(199946)		
HU 9900263	A2	19990928	(199946)		
ZA 9900678	A	19991027	(199951)		25
JP 11269193	A	19991005	(199953)		8
CA 2260315	A1	19990813	(200004)	EN	
SK 9900150	A3	20000118	(200018)		
CN 1239718	A	19991229	(200019)		
BR 9900442	A	20000502	(200033)		
NZ 334087	A	20000728	(200043)		
KR 99072345	A	19990927	(200048)		
US 6165985	A	20001226	(200103)		
MX 9901491	A1	20000201	(200123)		
IL 128238	A	20010913	(200158)		
NO 310917	B1	20010917	(200158)		
AU 748670	B	20020606	(200249)		
HU 222539	B1	20030828	(200363)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
DE 19805822	A1		DE 1998-19805822	19980213
EP 937734	A1		EP 1999-101675	19990208
NO 9900675	A		NO 1999-675	19990212
CZ 9900458	A3		CZ 1999-458	19990210
AU 9916438	A		AU 1999-16438	19990212
HU 9900263	A2		HU 1999-263	19990205
ZA 9900678	A		ZA 1999-678	19990128
JP 11269193	A		JP 1999-32750	19990210
CA 2260315	A1		CA 1999-2260315	19990125
SK 9900150	A3		SK 1999-150	19990205
CN 1239718	A		CN 1999-102126	19990211
BR 9900442	A		BR 1999-442	19990210
NZ 334087	A		NZ 1999-334087	19990208
KR 99072345	A		KR 1999-3207	19990201
US 6165985	A	CIP of	US 1999-247605	19990210
			US 1999-338602	19990623
MX 9901491	A1		MX 1999-1491	19990212
IL 128238	A		IL 1999-128238	19990126
NO 310917	B1		NO 1999-675	19990212
AU 748670	B		AU 1999-16438	19990212
HU 222539	B1		HU 1999-263	19990205

FILING DETAILS:

PATENT NO	KIND		PATENT NO

NO 310917 B1 Previous Publ. NO 9900675
AU 748670 B Previous Publ. AU 9916438

PRIORITY APPLN. INFO: DE 1998-19805822 19980213
AN 1999-509364 [43] WPIDS
AB DE 19805822 A UPAB: 19991020
NOVELTY - (2R,3S,4S,5R,6R,10R,11R)-2,4,6,8,10-Pentamethyl-11-acetyl-12,13-dioxabicyclo(8.2.1)tridec-8-en-1-one compounds are new.

DETAILED DESCRIPTION - (2R,3S,4S,5R,6R,10R,11R)-2,4,6,8,10-pentamethyl-11-acetyl-12,13- dioxabicyclo(8.2.1)tridec-8-en-1-one compounds of formula (I) and their acid addition salts are new
R1 = H or Me;
R2 = H or lower alkanoyl.

ACTIVITY - None given.

MECHANISM OF ACTION - Motilin agonist. In tests to determine displacement of radioactively labeled iodinated motilin from **motilin receptors** (using a modification of the method described in Regulatory Peptides 15 (1986), 143-153, the compound (2R,3S,4S,5R,6R,10R,11R)-3-((2,6-dideoxy-3-C-methyl-3-O-methyl- alpha -L-ribohexopyranosyl)-oxy)-5-((3,4,6-trideoxy-3-(N-methyl-N-isopropylamino)- beta -D-xylohexopyranosyl)-oxy)-2,4,6,8,10-pentamethyl-11-acetyl-12,13-dioxabicyclo(8.2.1)-tridec-8-en-1-one(Ia) exhibited a pIC50 value of 8.01 (no units given).

USE - (I) enhance gastrointestinal motility and may be used in treatment of motility disorders such as gastroesophageal reflux, dyspepsia, post-operative motility disorders, disorders of stomach evacuation, gastroparesis and disorders of stomach rhythm.

ADVANTAGE - (I) exhibit good oral activity and high selectivity for **motilin receptors.** At doses at which they are active as motilin agonists, they do not show appreciable affinity for other receptors in the gastrointestinal tract, such as histamine, dopamine or serotonin receptors. They exhibit excellent liver tolerability, making them suitable for long term use. They do not have antibiotic activity.
Dwg.0/0

L19 ANSWER 133 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:447202 SCISEARCH
THE GENUINE ARTICLE: 187GJ
TITLE: The motilide ABT-299 selectively downregulates **motilin receptors** in different tissues. Evidence for **motilin receptor** subtyes.
AUTHOR: Depoortere I (Reprint); Verlinden M; Thijs T; VanAssche G
CORPORATE SOURCE: KATHOLIEKE UNIV LEUVEN, LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1999) Vol. 116, No. 4, Part 2, pp. G4610-G4610.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 134 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:445333 SCISEARCH
THE GENUINE ARTICLE: 187GJ
TITLE: **Motilin receptors** of the rabbit colon.
AUTHOR: Miller P (Reprint); Trudel L; StPierre S; Poitras P
CORPORATE SOURCE: UNIV MONTREAL, CHUM ST LUC, MONTREAL, PQ, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1999) Vol. 116, No. 4, Part 2, pp. G2741-G2741.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST

CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 135 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:445332 SCISEARCH
THE GENUINE ARTICLE: 187GJ
TITLE: Search for **motilin receptors** on vagus nerves.
AUTHOR: Miller P (Reprint); Trudel L; Butterworth R; Huet P M; Sharkey K; Rocheleau B; Ho W; Poitras P
CORPORATE SOURCE: UNIV MONTREAL, CHUM ST LUC, MONTREAL, PQ, CANADA; UNIV CALGARY, CALGARY, AB, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1999) Vol. 116, No. 4, Part 2, pp. G2740-G2740.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 136 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:445331 SCISEARCH
THE GENUINE ARTICLE: 187GJ
TITLE: **Motilin receptors** in human gastrointestinal tract.
AUTHOR: Miller P (Reprint); Roy A; Dagenais M; Lapointe R; Serge S P; Poitras P
CORPORATE SOURCE: UNIV MONTREAL, CHUM ST LUC, MONTREAL, PQ, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1999) Vol. 116, No. 4, Part 2, pp. G2739-G2739.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 137 OF 391 MEDLINE on STN DUPLICATE 62
ACCESSION NUMBER: 1999316084 MEDLINE
DOCUMENT NUMBER: 99316084 PubMed ID: 10381885
TITLE: Receptor for motilin identified in the human gastrointestinal system.
AUTHOR: Feighner S D; Tan C P; McKee K K; Palyha O C; Hreniuk D L; Pong S S; Austin C P; Figueroa D; MacNeil D; Cascieri M A; Nargund R; Bakshi R; Abramovitz M; Stocco R; Kargman S; O'Neill G; Van Der Ploeg L H; Evans J; Patchett A A; Smith R G; Howard A D
CORPORATE SOURCE: Department of Metabolic Disorders, Department of Medicinal Chemistry, Merck Research Laboratories, Building RY-80Y-265, 126 East Lincoln Avenue, Rahway, NJ 07065, USA.
SOURCE: SCIENCE, (1999 Jun 25) 284 (5423) 2184-8.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990727
Last Updated on STN: 20000303
Entered Medline: 19990715

AB Motilin is a 22-amino acid peptide hormone expressed throughout the gastrointestinal (GI) tract of humans and other species. It affects gastric motility by stimulating interdigestive antrum and duodenal contractions. A heterotrimeric guanosine triphosphate-binding protein (G protein)-coupled receptor for motilin was isolated from human stomach, and its amino acid sequence was found to be 52 percent identical to the human receptor for growth hormone secretagogues. The macrolide antibiotic erythromycin also interacted with the cloned **motilin receptor**, providing a molecular basis for its effects on the human GI tract. The **motilin receptor** is expressed in enteric neurons of the human duodenum and colon. Development of **motilin receptor** agonists and antagonists may be useful in the treatment of multiple disorders of GI motility.

L19 ANSWER 138 OF 391 MEDLINE on STN DUPLICATE 63
ACCESSION NUMBER: 2000072980 MEDLINE
DOCUMENT NUMBER: 20072980 PubMed ID: 10605054
TITLE: Structure-activity study of intact porcine motilin.
AUTHOR: Haramura M; Tsuzuki K; Okamachi A; Yogo K; Ikuta M; Kozono T; Takanashi H; Murayama E
CORPORATE SOURCE: Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan.
SOURCE: CHEMICAL AND PHARMACEUTICAL BULLETIN, (1999 Nov) 47 (11) 1555-9.
Journal code: 0377775. ISSN: 0009-2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB Biologically important sites on intact porcine motilin (pMTL) were explored using its partial peptides. The partial peptides were synthesized using Fmoc (9-fluorenylmethyloxycarbonyl) solid phase methodology, and tested for the binding activity to **motilin receptor** and the smooth muscle contractile activity. The results were as follows: important residues for the contractile activity were found to be Phe1, Ile4, and Tyr7, and an open space existed beyond the N-terminus between motilin and its receptor. On the model of interaction between motilin and **motilin receptor** evolved from these results, the three points of interaction, due to Phe1, Ile4, and Tyr7, and the presence of an open space were expected. The motilin agonist and antagonist, designed on this model, will help the inquiry into motilin associated diseases.

L19 ANSWER 139 OF 391 MEDLINE on STN DUPLICATE 64
ACCESSION NUMBER: 1999316541 MEDLINE
DOCUMENT NUMBER: 99316541 PubMed ID: 10389679
TITLE: Effect of EM574 on postprandial pancreaticobiliary secretion, gastric motor activity, and emptying in conscious dogs.
AUTHOR: Tanaka T; Mizumoto A; Mochiki E; Suzuki H; Itoh Z; Omura S
CORPORATE SOURCE: Gastrointestinal Research Laboratory, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Japan.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (1999 Jun) 44 (6) 1100-6.
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990727
Last Updated on STN: 19990727
Entered Medline: 19990715

AB EM574, an erythromycin derivative and a potent **motilin receptor** agonist, is now under clinical trial as a gastroprokinetic drug. The aim of this study was to estimate the effect of EM574 on postprandial pancreaticobiliary secretion, gastric motor activity, and emptying in conscious dogs. Five mongrel dogs were prepared. Indwelling cannulas for both infusion of phenolsulfonphthalein and aspiration of luminal samples were inserted into the proximal and distal duodenum, respectively. EM574 (3-30 microg/kg) was given intraduodenally through the indwelling distal duodenal cannula at the start of feeding. Postprandial pancreatic and biliary secretions were assessed by measuring the outputs of amylase and bile acid into the duodenum, respectively. Gastric motor and emptying activity were measured by means of a force transducer method and our own freeze-drying method, respectively. One hundred grams of a freeze-dried standard meal was given as a solid marker after being mixed with 100 ml of normal saline containing 15 g of polyethylene glycol as a liquid marker. EM574 at doses of 10 and 30 microg/kg significantly increased the mean integrated postprandial amylase output into the duodenum, but the mean integrated postprandial bile acid output was not significantly increased. EM574 increased postprandial gastric antral motor activity dose-dependently. EM574 at doses of 10 and 30 microg/kg significantly accelerated gastric emptying of liquids and solids, respectively. EM574 enhances gastric antral motor activity and accelerates gastric emptying of solids and liquids with a concomitant increase in postprandial pancreatic amylase, but not bile acid, output in normal dogs.

L19 ANSWER 140 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:329552 BIOSIS
DOCUMENT NUMBER: PREV199900329552
TITLE: The motilide ABT-299 selectively downregulates **motilin receptors** in different tissues. Evidence for **motilin receptor** subtypes.
AUTHOR(S): Depoortere, I. [Reprint author]; Verlinden, M.; Thijs, T.; Van Assche, G.; Peeters, Theo
CORPORATE SOURCE: Univ of Leuven, Leuven, Belgium
SOURCE: Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A1061. print.
Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association. Orlando, Florida, USA. May 16-19, 1999. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Aug 1999
Last Updated on STN: 24 Aug 1999

L19 ANSWER 141 OF 391 MEDLINE on STN DUPLICATE 65
ACCESSION NUMBER: 1999145339 MEDLINE
DOCUMENT NUMBER: 99145339 PubMed ID: 10022741
TITLE: A direct inhibitory effect of erythromycin on rat urinary bladder smooth muscle.
AUTHOR: Nissan A; Maudlej N; Beglaibter N; Haskel Y; Freund H R; Hanani M
CORPORATE SOURCE: Department of Surgery, Hadassah University Hospital, Mount Scopus, Hebrew University-Hadassah Medical School, Jerusalem, Israel.
SOURCE: JOURNAL OF UROLOGY, (1999 Mar) 161 (3) 1006-9.

Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990324
Last Updated on STN: 19990324
Entered Medline: 19990311

AB Erythromycin (EM) exerts a dual effect on the contractility of smooth muscle. An excitatory effect mediated via **motilin receptors** is expressed mainly in the smooth muscle of the stomach and duodenum. The other, a direct inhibitory effect mediated via an unknown mechanism, has been described in guinea-pig and human gallbladder, in the longitudinal smooth muscle of the guinea-pig small intestine and in bronchial smooth muscle. In the present study, the effect of EM on the isolated urinary bladder of the rat was examined using isometric force measurements. The muscarinic agonist carbachol evoked contractions that were reduced by EM in a concentration-dependent manner; at 5 x 10(4) M by 46% [from 1.04+/-0.42 gm. to 0.56+/-0.22 gm., (p <0.001)] and at 10(-3) M by 57% [from 1.04+/-0.42 gm. to 0.45+/-0.20 gm., (p <0.001)]. The inhibitory effect of EM was not altered by the nerve blocker tetrodotoxin. Electric field stimulation of 0.5 Hz, 1 Hz, and 2 Hz contracted the urinary bladder. Erythromycin at 5 x 10(-4) M reduced the contractions evoked at 0.5 Hz by 15% [from 0.60+/-0.22 gm. to 0.51+/-0.20 gm., (p = 0.004)] and at 10(-3) M by 23% [from 0.60+/-0.22 gm. to 0.46+/-0.12 gm., (p <0.001)]. Erythromycin failed to affect the contractions evoked by bradykinin, phenylephrine or substance P. It is concluded that EM has a direct inhibitory effect on the rat urinary bladder smooth muscle.

L19 ANSWER 142 OF 391 MEDLINE on STN DUPLICATE 66
ACCESSION NUMBER: 1999447680 MEDLINE
DOCUMENT NUMBER: 99447680 PubMed ID: 10517907
TITLE: Effect of different prokinetic agents and a novel enterokinetic agent on postoperative ileus in rats.
AUTHOR: De Winter B Y; Boeckxstaens G E; De Man J G; Moreels T G; Schuurkes J A; Peeters T L; Herman A G; Pelckmans P A
CORPORATE SOURCE: Division of Gastroenterology and Pharmacology, Faculty of Medical and Pharmaceutical Sciences, University of Antwerp, Wilrijk, Belgium.
SOURCE: GUT, (1999 Nov) 45 (5) 713-8.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991207

AB BACKGROUND/AIM: The effects of different prokinetic agents, the motilide erythromycin and the substituted benzamides metoclopramide and cisapride, were investigated in a rat model of postoperative ileus. These effects were compared with that of granisetron, a 5-hydroxytryptamine (5-HT(3)) receptor antagonist, and a novel enterokinetic agent, prucalopride, a 5-HT(4) receptor agonist. METHODS: Different degrees of inhibition of gastrointestinal transit, measured by the migration of Evans blue, were achieved by skin incision, laparotomy, or laparotomy plus mechanical stimulation of the gut. RESULTS: Metoclopramide decreased the transit after laparotomy with or without mechanical stimulation, whereas cisapride increased it after all three operations. Granisetron had no effect on the transit after the three operations when given alone. Prucalopride tended to increase the transit after laparotomy with or without mechanical stimulation when given alone. However, statistical significance was only reached when prucalopride was combined with granisetron. Erythromycin, a

motilin receptor agonist, did not improve postoperative ileus in the rat. CONCLUSIONS: Cisapride, but not metoclopramide or erythromycin, is able to improve postoperative ileus in the rat. The results suggest that a combination of 5-HT(3) receptor antagonist and 5-HT(4) receptor agonist properties may be required to obtain a beneficial effect on surgery induced ileus in the rat. Furthermore, they indirectly indicate that stimulation of the excitatory mechanisms is not able to overcome the inhibitory influence of the neural reflex pathways activated during abdominal surgery.

L19 ANSWER 143 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:291065 BIOSIS
DOCUMENT NUMBER: PREV199900291065
TITLE: **Motilin receptors** in human gastrointestinal tract.
AUTHOR(S): Miller, Paul [Reprint author]; Roy, Andre [Reprint author]; Dagenais, Michel [Reprint author]; Lapointe, Real [Reprint author]; Serge, St-Pierre [Reprint author]; Poitras, Pierre [Reprint author]
CORPORATE SOURCE: CHUM, Saint-Luc - Univsite de Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A627. print.
Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association. Orlando, Florida, USA. May 16-19, 1999. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1999
Last Updated on STN: 5 Aug 1999

L19 ANSWER 144 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:291067 BIOSIS
DOCUMENT NUMBER: PREV199900291067
TITLE: **Motilin receptors** of the rabbit colon.
AUTHOR(S): Miller, Paul [Reprint author]; Trudel, Louise [Reprint author]; St-Pierre, Serge [Reprint author]; Poitras, Pierre [Reprint author]
CORPORATE SOURCE: CHUM, Saint-Luc - Univsite de Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A627. print.
Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association. Orlando, Florida, USA. May 16-19, 1999. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1999
Last Updated on STN: 5 Aug 1999

L19 ANSWER 145 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:291066 BIOSIS
DOCUMENT NUMBER: PREV199900291066
TITLE: Search for **motilin receptors** on vagus nerves.
AUTHOR(S): Miller, Paul [Reprint author]; Trudel, Louise [Reprint author]; Butterworth, Roger [Reprint author]; Huet, Pierre-Michel [Reprint author]; Sharkey, Keith; Rocheleau, Bernard; Ho, Winnie; Poitras, Pierre

CORPORATE SOURCE: CHUM, Saint-Luc - Univsite de Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A627. print.
Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association. Orlando, Florida, USA. May 16-19, 1999. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1999
Last Updated on STN: 5 Aug 1999

L19 ANSWER 146 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:675220 SCISEARCH
THE GENUINE ARTICLE: 230QF
TITLE: Erythromycin-responsive **motilin receptor** regulates upper gastrointestinal motility
AUTHOR: Gordon D
SOURCE: GASTROENTEROLOGY, (SEP 1999) Vol. 117, No. 3, pp. 524-524.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: News Announcement; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 147 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:48480 BIOSIS
DOCUMENT NUMBER: PREV200000048480
TITLE: An orphan G protein-coupled receptor found in the human gastrointestinal system is identified as a **motilin receptor.**
AUTHOR(S): Hreniuk, D. [Reprint author]; Howard, A. [Reprint author]; Tan, C. [Reprint author]; McKee, K. [Reprint author]; Palyha, O. [Reprint author]; Pong, S. S. [Reprint author]; Austin, C.; Figureoa, D.; Nargund, R.; Bakshi, R.; Hong, Q.; Abramovitz, M.; Stocco, R.; Kargman, S.; O'Neill, G.; Van Der Pleog, L.H.T. [Reprint author]; Evans, J.; Patchett, A.; Smith, R.; Feighner, S. [Reprint author]
CORPORATE SOURCE: Dept. of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, USA
SOURCE: Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 433. print.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience, Part 1. Miami Beach, Florida, USA. October 23-28, 1999. The Society for Neuroscience.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Feb 2000
Last Updated on STN: 31 Dec 2001

L19 ANSWER 148 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 67
ACCESSION NUMBER: 2000:40955 BIOSIS
DOCUMENT NUMBER: PREV200000040955
TITLE: **Motilin receptor** agonists as novel gastrointestinal prokinetic agents.
AUTHOR(S): Salat, Pinky; Parikh, Vinay [Reprint author]
CORPORATE SOURCE: Sun Pharma Advanced Research Centre, Akota Road, Akota,

Vadodara, GUJ, 390020, India
SOURCE: Indian Journal of Pharmacology, (Oct., 1999) Vol. 31, No. 5, pp. 333-339. print.
CODEN: INJPD2. ISSN: 0253-7613.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jan 2000
Last Updated on STN: 31 Dec 2001

AB Motilin is a naturally occurring gastrointestinal (GI) polypeptide which stimulates GI smooth muscle contractility through **motilin receptors.** Motilides are members of macrolide family which exhibit prokinetic activity by acting as **motilin receptor** agonists but lack antibacterial activity. The mechanism for smooth muscle contractile effect of motilin/motilides involve activation of voltage sensitive Ca2+ channels and release of Ca2+ from intracellular Ca2+ stores via G protein linked phospholipase C/inositol 1,4,5 trisphosphate pathway. None of the currently available drugs qualify as an ideal prokinetic agent due to variable efficacy and side effects. Motilides possess potent gastroprokinetic activity and do not produce side effects. They may be considered as drugs of choice for the treatment of various GI functional motor disorders like gastro-oesophageal reflux disease, gastroparesis, postoperative ileus, scleroderma and idiopathic pseudo-obstruction.

L19 ANSWER 149 OF 391 MEDLINE on STN DUPLICATE 68
ACCESSION NUMBER: 1999396070 MEDLINE
DOCUMENT NUMBER: 99396070 PubMed ID: 10467994
TITLE: Effect of sequential erythromycin and octreotide on antroduodenal manometry.
AUTHOR: Di Lorenzo C; Lucanto C; Flores A F; Idries S; Hyman P E
CORPORATE SOURCE: Department of Pediatrics, Children's Hospital of Pittsburgh, Pennsylvania 15213, USA.
SOURCE: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, (1999 Sep) 29 (3) 293-6.
Journal code: 8211545. ISSN: 0277-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991004

AB BACKGROUND: In earlier studies, erythromycin stimulated but octreotide inhibited gastric antral contractions, as each drug induced phase 3-like episodes. METHODS: To assess the effect of erythromycin pretreatment on octreotide-induced changes in antroduodenal motility, 16 patients were studied (mean age, 8.7 +/- 1.5 years, 8 male): 6 with severe gastroesophageal reflux, 4 with cyclic vomiting, 3 with gastroparesis, 2 with chronic intestinal pseudo-obstruction, and 1 with Crohn's disease and unexplained nausea and vomiting. After recording fasting antroduodenal motility for 3 hours, 1 mg/kg intravenous erythromycin was administered over 30 minutes. Sixty minutes after the erythromycin infusion, 0.5 microg/kg subcutaneous octreotide was administered, followed 1 hour later by a meal. RESULTS: Phase 3 occurred spontaneously in 10 patients and after erythromycin in 12 patients. When administered after erythromycin, octreotide immediately induced phase 3s contractions in 15 patients, beginning in the antrum. In 7 children, some of the octreotide-induced phase 3s did not propagate. After the meal, antral contractions continued in all patients. The fed pattern was replaced in 14 patients by alternating phase 3 and phase 1 activities. CONCLUSIONS: Pretreatment with erythromycin prevented octreotide-induced inhibition of antral contractions. Inhibition of antral contractions by octreotide may be mediated through either a direct or indirect suppression of motilin

release, because antral contractions persist after pretreatment with the **motilin receptor** agonist erythromycin.

L19 ANSWER 150 OF 391 MEDLINE on STN DUPLICATE 69
ACCESSION NUMBER: 1999181462 MEDLINE
DOCUMENT NUMBER: 99181462 PubMed ID: 10081621
TITLE: Erythromycin derivatives ABT 229 and GM 611 act on **motilin receptors** in the rabbit duodenum.
AUTHOR: Clark M J; Wright T; Bertrand P P; Bornstein J C; Jenkinson K M; Verlinden M; Furness J B
CORPORATE SOURCE: Department of Anatomy and Cell Biology, University of Melbourne, Parkville, Victoria, Australia.
SOURCE: CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY, (1999 Mar) 26 (3) 242-5.
Journal code: 0425076. ISSN: 0305-1870.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990518

AB 1. The present study was undertaken to determine whether the macrolide antibiotic erythromycin, its stable motilide derivatives ABT 229 and GM 611 and motilin act at the same receptors on intestinal muscle 2. Each compound contracted the longitudinal muscle of the rabbit duodenum in a concentration-dependent manner that was unaffected by 1 mumol/L tetrodotoxin. The potency order (pEC50 values in brackets) was motilin (8.4), ABT 229 (7.6), GM 611 (7.5) and erythromycin (6.0). 3. The **motilin receptor** antagonists GM 109 and [phe3, leu13]-motilin, both shifted the concentration-response curves for each agonist to the right, but did not affect concentration-response relationships for the muscarinic agonist carbachol. Schild regression analysis yielded similar pA2 values for GM 109 (in the range 7.2-7.5) for all agonists. This analysis was not done for [phe3, leu13]motilin, which was a non-competitive antagonist and partial agonist. 4. It is concluded that erythromycin, the motilides and motilin act at the same (**motilin**) **receptor** on rabbit duodenal muscle and do not have any detectable actions at other receptors in this preparation.

L19 ANSWER 151 OF 391 MEDLINE on STN DUPLICATE 70
ACCESSION NUMBER: 2000162769 MEDLINE
DOCUMENT NUMBER: 20162769 PubMed ID: 10697661
TITLE: Novel approaches to the treatment of nausea and vomiting.
AUTHOR: Ladabaum U; Hasler W L
CORPORATE SOURCE: Division of Gastroenterology, University of California, San Francisco, USA.
SOURCE: DIGESTIVE DISEASES, (1999) 17 (3) 125-32. Ref: 73
Journal code: 8701186. ISSN: 0257-2753.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309

AB Nausea and vomiting are debilitating symptoms complicating many clinical conditions. Conventional antiemetic agents act as muscarinic, histamine, and dopamine receptor antagonists in the central nervous system. In a retrospective analysis, tricyclic antidepressant drugs demonstrated efficacy in long-term treatment of functional nausea. Some cases of

vomiting result from impaired gastrointestinal motor activity. Agents which act on gastric serotonin (5-HT4), dopamine, and **motilin receptors** accelerate gastric emptying and relieve symptoms in gastroparesis. Recent investigations suggest that some patients with refractory gastroparesis may benefit from gastric electrical pacing. The treatment of acute chemotherapy-induced emesis was revolutionized by 5-HT3 receptor antagonists; however, these agents are less efficacious in delayed vomiting. Neurokinin (NK-1) receptor antagonists show promise in treating delayed chemotherapy-evoked emesis. Furthermore, animal studies indicate a broad spectrum of action for NK-1 antagonists in treating diverse causes of nausea and vomiting. The cyclic vomiting syndrome is characterized by discrete episodes of relentless vomiting separated by asymptomatic intervals and is associated with migraine headaches. Antimigraine therapies including the 5-HT1D receptor agonists sumatriptan reduce the severity of cyclic vomiting attacks. Investigations into these and other novel treatments may provide important advances in the care of difficult cases of nausea and vomiting resulting from disparate illnesses.

L19 ANSWER 152 OF 391 MEDLINE on STN DUPLICATE 71
ACCESSION NUMBER: 2000039352 MEDLINE
DOCUMENT NUMBER: 20039352 PubMed ID: 10574195
TITLE: Application of liquid chromatography-turbo ion spray tandem mass spectrometry for quantitative analysis of a potent **motilin receptor** agonist, EM574, and its metabolites in human plasma.
AUTHOR: Kondo T; Dote N; Hagimoto T; Yoshimura Y
CORPORATE SOURCE: Drug Analysis and Pharmacokinetics Research Laboratories, Takeda Chemical Industries Ltd., Osaka, Japan.. kondo_takahiro@takeda.co.jp
SOURCE: JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND APPLICATIONS, (1999 Oct 29) 734 (1) 101-12. Journal code: 9714109. ISSN: 1387-2273.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991202
AB A liquid chromatography-tandem mass spectrometry (LC-MS-MS) method for the simultaneous determination of a new potent **motilin receptor** agonist as erythromycin derivative, EM574 (erythromycin derivative), and its three metabolites, M-IV, M-V and M-VI, in human plasma was developed. The internal standards (I.S.s) used were deuterated EM574, M-IV and M-V. For the quantitation of M-VI, deuterated M-V was used. The analytes and I.S. were extracted from plasma samples with diethyl ether at neutral pH. A turbo ion spray interface was used as the ion source of LC-MS-MS, and the analysis was performed in the selected reaction monitoring mode. The lower quantitation limits for all the analytes were 0.05 ng/ml when 0.2 ml of plasma was used, and the standard curves were linear in the range 0.05 to 20 ng/ml. The method was precise; the intra- and inter-day precisions of the method were not more than 19.8% for all the analytes. The accuracy of the method was good with the deviations between added and calculated concentrations of each analyte being typically within +/- 11.2%.

L19 ANSWER 153 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1999:864957 SCISEARCH
THE GENUINE ARTICLE: 253EM
TITLE: Application of liquid chromatography-turbo ion spray tandem mass spectrometry for quantitative analysis of a potent **motilin receptor** agonist, EM574, and its metabolites in human plasma
AUTHOR: Kondo T (Reprint); Dote N; Hagimoto T; Yoshimura Y

CORPORATE SOURCE: TAKEDA CHEM IND LTD, DIV PHARMACEUT RES, DRUG ANAL & PHARMACOKINET RES LABS, YODOGAWA KU, OSAKA 5328686, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF CHROMATOGRAPHY B, (29 OCT 1999) Vol. 734, No. 1, pp. 101-112.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0378-4347.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 12

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A liquid chromatography-tandem mass spectrometry (LC-MS-MS) method for the simultaneous determination of a new potent **motilin receptor** agonist as erythromycin derivative, EM574 (erythromycin derivative), and its three metabolites, M-IV, M-V and M-VI, in human plasma was developed. The internal standards (I.S.s) used were deuterated EM574, M-IV and M-V. For the quantitation of M-VI, deuterated M-V was used. The analytes and I.S. were extracted from plasma samples with diethyl ether at neutral pH. A turbo ion spray interface was used as the ion source of LC-MS-MS, and the analysis was performed in the selected reaction monitoring mode. The lower quantitation limits for all the analytes were 0.05 ng/ml when 0.2 mi of plasma was used, and the standard curves were linear in the range 0.05 to 20 ng/ml. The method was precise; the intra- and inter-day precisions of the method were not more than 19.8% for all the analytes. The accuracy of the method was good with the deviations between added and calculated concentrations of each analyte being typically within +/-11.2%. (C) 1999 Elsevier Science B.V. All rights reserved.

L19 ANSWER 154 OF 391 MEDLINE on STN DUPLICATE 72
ACCESSION NUMBER: 1999164722 MEDLINE
DOCUMENT NUMBER: 99164722 PubMed ID: 10065328
TITLE: An action of erythromycin in the intestine that is not mediated via **motilin receptors.**
AUTHOR: Furness J B; Clark M J; Wright T; Bertrand P P; Bornstein J C; Verlinden M
CORPORATE SOURCE: Department of Anatomy and Cell Biology, University of Melbourne, Parkville, Victoria, Australia.. john.furness@anatomy.unimelb.edu.au
SOURCE: CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY, (1999 Feb) 26 (2) 100-4.
Journal code: 0425076. ISSN: 0305-1870.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990609

AB 1. Erythromycin lactobionate caused a concentration-dependent inhibition of nerve-mediated contractions of the longitudinal muscle of the guinea-pig ileum, with a threshold for effect of 10-30 mumol/L. The non-antibiotic derivative of erythromycin ABT-229 had a similar effect, but was approximately 10-fold less potent. At a greater concentration (1 mmol/L), erythromycin also depressed the direct contractile effect of 10 mumol/L carbachol on the muscle. 2. Human/porcine motilin (up to 100 mumol/L) did not reduce the nerve-mediated contractions, although it did contract the muscle (threshold 30 mumol/L). Antagonists of **motilin receptors** (phe3leu13motilin, up to 1 mumol/L, and GM-109, up to 3 mumol/L) did not reduce responses to erythromycin. 3. Erythromycin contracted the longitudinal muscle of the rabbit duodenum,

with a threshold concentration of 0.1 mumol/L and ABT-229 contracted this tissue at a threshold concentration of 0.01 mumol/L. Effects of both agonists were antagonized by the **motilin receptor** antagonists phe3leu13motilin (0.3 mumol/L) and GM-109 (1 mumol/L). 4. It is concluded that the site(s) at which erythromycin acts in the guinea-pig ileum is not a **motilin receptor** and that ABT-229 is selective for the **motilin receptor** in comparison with non-motilin erythromycin sites and is unlikely to act at the latter site in therapeutic doses.

L19 ANSWER 155 OF 391 MEDLINE on STN
ACCESSION NUMBER: 1999219992 MEDLINE
DOCUMENT NUMBER: 99219992 PubMed ID: 10202210
TITLE: Management of irritable bowel syndrome: novel approaches to the pharmacology of gut motility.
AUTHOR: Scarpignato C; Pelosini I
CORPORATE SOURCE: Department of Gastroenterology and Hepatology, Faculty of Medicine, University of Nantes, France.. scarpi@tin.it
SOURCE: CANADIAN JOURNAL OF GASTROENTEROLOGY, (1999 Mar) 13 Suppl A 50A-65A. Ref: 169
Journal code: 8807867. ISSN: 0835-7900.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990517

AB Although it is unclear to what extent irritable bowel syndrome (IBS) symptoms represent a normal perception of abnormal function or an abnormal perception of normal function, many believe that IBS constitutes the clinical expression of an underlying motility disorder, affecting primarily the mid- and lower gut. Indeed, transit and contractile abnormalities have been demonstrated with sophisticated techniques in a subset of patients with IBS. As a consequence, drugs affecting gastrointestinal (GI) motility have been widely employed with the aim of correcting the major IBS manifestations, ie, pain and altered bowel function. Unfortunately, no single drug has proven to be effective in treating IBS symptom complex. In addition, the use of some medications has often been associated with unpleasant side effects. Therefore, the search for a truly effective and safe drug to control motility disturbances in IBS continues. Several classes of drugs look promising and are under evaluation. Among the motor-inhibiting drugs, gut selective muscarinic antagonists (such as zamifenacin and darifenacin), neurokinin2 antagonists (such as MEN-10627 and MEN-11420), beta3-adrenoreceptor agonists (eg, SR-58611A) and GI-selective calcium channel blockers (eg, pinaverium bromide and octylonium) are able to decrease painful contractile activity in the gut (antispasmodic effect), without significantly affecting other body functions. Novel mechanisms to stimulate GI motility and transit include blockade of cholecystokinin (CCK)A receptors and stimulation of **motilin receptors.** Loxiglumide (and its dextroisomer, dexloxiglumide) is the only CCKA receptor antagonist that is being evaluated clinically. This drug accelerates gastric emptying and colonic transit, thereby increasing the number of bowel movements in patients with chronic constipation. It is also able to reduce visceral perception. Erythromycin and related 14-member macrolide compounds inhibit the binding of motilin to its receptors on GI smooth muscle and, therefore, act as motilin agonists. This antibiotic accelerates gastric emptying and shortens orocecal transit time. In the large bowel a significant decrease in transit is observed only in the right colon, which suggests a shift in fecal distribution. Several 'motilinomimetics' have been synthesized. Their development

depends on the lack of antimicrobial activity and the absence of fading of the prokinetic effect during prolonged administration. 5-hydroxytryptamine (5-HT)4 agonists with significant pharmacological effects on the mid- and distal gut (such as prucalopride and tegaserod) are available for human use. These 'enterokinetic' compounds are useful for treating constipation-predominant IBS patients. 5-HT3 receptor antagonists also possess a number of interesting pharmacological properties that may make them suitable for treatment of IBS. Besides decreasing colonic sensitivity to distension, these drugs prolong intestinal transit and may be particularly useful in diarrhea-predominant IBS. Finally, when administered in small pulsed doses, octreotide, besides reducing the perception of rectal distension, accelerates intestinal transit, although other evidence disputes such an effect.

L19 ANSWER 156 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:70173 SCISEARCH
THE GENUINE ARTICLE: 268MN
TITLE: Molecular identification of the **motilin receptor**, a G-protein-coupled receptor related to the orphan receptor for growth hormone secretagogues
AUTHOR: Howard A D (Reprint); Tan C P; McKee K K; Palyha O C; Hreniuk D L; Pong S S; Austin C P; Figureoa D; MacNeil D; Cascieri M A; Nargund R; Bakshi R; Abramovitz M; Stocco R; Kargman S; ONeill G; VanderPloeg L H T; Evans J; Patchett A A; Smith R G; Feighner S D
CORPORATE SOURCE: MERCK RES LABS, DEPT METAB DISORDERS, RAHWAY, NJ 07065; MERCK RES LABS, DEPT MED CHEM, RAHWAY, NJ 07065; MERCK RES LABS, DEPT HUMAN GENET, W POINT, PA 19486; MERCK FROSST CTR THERAPEUT RES, DEPT BIOCHEM & MOL BIOL, KIRKLAND, PQ H9H 3L1, CANADA; BAYLOR COLL MED, HUFFINGTON CTR AGING, HOUSTON, TX 77030; BAYLOR COLL MED, DEPT CELL BIOL, HOUSTON, TX 77030
COUNTRY OF AUTHOR: USA; CANADA
SOURCE: BRAIN RESEARCH, (27 NOV 1999) Vol. 848, No. 1-2, pp. 46-46
.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0006-8993.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 157 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:177617 BIOSIS
DOCUMENT NUMBER: PREV200000177617
TITLE: Molecular identification of the **motilin receptor**, a G-protein-coupled receptor related to the orphan receptor for growth hormone secretagogues.
AUTHOR(S): Howard, Andrew D. [Reprint author]; Tan, Carina P. [Reprint author]; McKee, Karen Kulju [Reprint author]; Palyha, Oksana C. [Reprint author]; Hreniuk, Donna L. [Reprint author]; Pong, Sheng-Shung [Reprint author]; Austin, Christopher P.; Figureoa, David; MacNeil, Douglas [Reprint author]; Cascieri, Margaret A. [Reprint author]; Nargund, Ravi; Bakshi, Raman; Abramovitz, Mark; Stocco, Rino; Kargman, Stacia; O'Neill, Gary; Van der Ploeg, Lex H. T. [Reprint author]; Evans, Jilly; Patchett, Arthur A.; Smith, Roy G.; Feighner, Scott D. [Reprint author]
CORPORATE SOURCE: Dept. of Metabolic Disorders, Merck Research Laboratories, Building RY-80Y-265, Rahway, NJ, 07065, USA
SOURCE: Brain Research, (Nov. 27, 1999) Vol. 848, No. 1-2, pp. A18. print.
Meeting Info.: 2nd Brain Research Interactive Sypmosium. Miami, FL, USA. October 21-23, 1999.

CODEN: BRREAP. ISSN: 0006-8993.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 11 May 2000
Last Updated on STN: 4 Jan 2002

L19 ANSWER 158 OF 391 MEDLINE on STN DUPLICATE 73
ACCESSION NUMBER: 1999411685 MEDLINE
DOCUMENT NUMBER: 99411685 PubMed ID: 10483884
TITLE: The ontogeny of the small intestinal epithelium.
AUTHOR: Lebenthal A; Lebenthal E
CORPORATE SOURCE: Department of Pediatrics, Mt Scopus, Hadassah University Hospital, Jerusalem, Israel.
SOURCE: JPEN. JOURNAL OF PARENTERAL AND ENTERAL NUTRITION, (1999 Sep-Oct) 23 (5 Suppl) S3-6. Ref: 21
Journal code: 7804134. ISSN: 0148-6071.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991108

AB The primary factors in feeding premature infants are dependent on the development and maturation of digestion and absorption. The maturation of digestive and absorptive functions of carbohydrates, proteins, fats, minerals, and vitamins in the young premature infant were determined in relation to availability of hydrolytic enzymes, such as lipases, proteases, amylases, glucosidases, and lactase. The feeding is dependent on the ability of the premature infant to secrete salivary enzymes, gastric acid, pepsin, pancreatic exocrine enzymes, the presence of enterohepatic circulation, and the hydrolytic and absorptive capacity of the entercocyte. To evaluate the complexity of the gut maturation process, we proposed a unified concept where the ontogeny of the gastrointestinal system is the result of the following four major determinants: genetic endowment, intrinsic developmental and biological clock, endogenous regulatory mechanisms, and environmental influences. The developmental clock represents a predetermined temporal sequence of happenings in ontogeny that is inherently controlled. By 20 weeks of gestation, the anatomic differentiation of the fetal gut has progressed to the extent that it resembles that of a newborn. Secretory and absorptive functions, however, develop at different rates; the intestinal absorptive process is only partially available before 26 weeks of gestation, whereas gastric and pancreatic secretion is only basal and can be stimulated only partially even in the full-term newborn period. Regulatory mechanisms control the expression of the genetic endowment at various stages in gastrointestinal development. Neural-hormonal factors play major roles in the ontogeny of the gut. Adrenalectomy, hypophysectomy, and thyroidectomy delay the development of the gut. Administration of glucocorticoids or thyroxine at the critical stage in maturation causes early appearance of enzymes within the intestine. Other hormones that are potentially important in regulating gastrointestinal development include cholecystokinin, gastrin, secretin, which have trophic effects on the gastrointestinal tract, and insulin, insulin-like growth factors, and epidermial growth factor. The development of gastrointestinal secretory function, particularly in response to hormonal stimulation, has received considerable attention. The degree of response of the target cell is determined not only by the amount of effective hormone reaching it but also by the number and affinity of receptors on its surface. Human newborns have high levels of gastrin in their sera, yet have low acid output. Exogenous gastrin is an ineffective stimulant despite the

presence of seemingly "anatomically developed" parietal cells. It seems that neither endogenous nor exogenous gastrin has an effect on the target cell. If one accepts the role of circulating gastrin levels in the regulation of its own receptor, one can hypothesize the absence of a regulatory effect of gastrin in the newborn period. It was shown that hormonal regulation of migrating activity by motilin is also absent in the preterm and term infant. Plasma levels of motilin in neonates are comparable to those found in adults, but migrating motor complexes occur in the absence of cycling of plasma concentrations. Interestingly, however, the **motilin receptor** appears to be present.
In conclusion, the feeding mode content, concentration, and volume of the very young premature infant can be assessed by the development of digestive and absorptive capacity and gut motility. The concomitant changes in gut hormones and regulatory peptides during ontogeny and feeding will add a new dimension in the understanding of when, what, and how to feed the very young premature infant.

L19 ANSWER 159 OF 391 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1998-232593 [21] WPIDS
DOC. NO. CPI: C1998-072673
TITLE: New hexa methyl-10,13,15-tri oxa-tri cyclo-penta decanone derivatives - useful as **motilin receptor** agonists in treatment of e.g. dyspepsia, gastric reflux and postoperative gastric motility disorders.
DERWENT CLASS: B02
INVENTOR(S): EECKHOUT, C; FINNER, E; HOLTJE, D; PREUSCHOFF, U; HOELTJE, D; PREU, U; HILTJE, D
PATENT ASSIGNEE(S): (SOLV) SOLVAY PHARM GMBH; (KALI) KALI-CHEMIE PHARMA GMBH
COUNTRY COUNT: 36
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 838469	A1	19980429	(199821)*	GE	12
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
DE 19644195	A1	19980430	(199823)		10
NO 9704934	A	19980427	(199826)		
SK 9701419	A3	19980506	(199826)		
AU 9742788	A	19980430	(199829)		
CZ 9703106	A3	19980617	(199830)		
JP 10130297	A	19980519	(199830)		9
ZA 9709059	A	19980729	(199835)		23
CA 2219311	A	19980424	(199836)		
HU 9701660	A2	19980528	(199838)		
NZ 328979	A	19981028	(199901)		
US 5912235	A	19990615	(199930)		
KR 98032626	A	19980725	(199932)		
MX 9707974	A1	19980401	(200004)		
BR 9705157	A	19990928	(200005)		
IL 121969	A	20000629	(200047)		
NO 308362	B1	20000904	(200051)		
AU 726092	B	20001102	(200062)		
BR 9705143	A	20001212	(200102)		
EP 838469	B1	20020109	(200211)	GE	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
DE 59705964	G	20020214	(200213)		
MX 199461	B	20001108	(200215)		
RU 2181727	C2	20020427	(200241)		
ES 2170318	T3	20020801	(200263)		
SK 283114	B6	20030204	(200318)		
TW 489088	A	20020601	(200319)		
CN 1186808	A	19980708	(200336)		
CZ 291768	B6	20030514	(200337)		
PH 1199758268	B1	20010914	(200357)		

HU 222540 B1 20030828 (200363)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 838469	A1	EP 1997-118000	19971017
DE 19644195	A1	DE 1996-19644195	19961024
NO 9704934	A	NO 1997-4934	19971024
SK 9701419	A3	SK 1997-1419	19971017
AU 9742788	A	AU 1997-42788	19971022
CZ 9703106	A3	CZ 1997-3106	19971001
JP 10130297	A	JP 1997-289861	19971022
ZA 9709059	A	ZA 1997-9059	19971009
CA 2219311	A	CA 1997-2219311	19971024
HU 9701660	A2	HU 1997-1660	19971017
NZ 328979	A	NZ 1997-328979	19971017
US 5912235	A	US 1997-954891	19971021
KR 98032626	A	KR 1997-51470	19971007
MX 9707974	A1	MX 1997-7974	19971016
BR 9705157	A	BR 1997-5157	19971024
IL 121969	A	IL 1997-121969	19971014
NO 308362	B1	NO 1997-4934	19971024
AU 726092	B	AU 1997-42788	19971022
BR 9705143	A	BR 1997-5143	19971024
EP 838469	B1	EP 1997-118000	19971017
DE 59705964	G	DE 1997-505964	19971017
		EP 1997-118000	19971017
MX 199461	B	MX 1997-7974	19971016
RU 2181727	C2	RU 1997-117347	19971023
ES 2170318	T3	EP 1997-118000	19971017
SK 283114	B6	SK 1997-1419	19971017
TW 489088	A	TW 1997-114816	19971009
CN 1186808	A	CN 1997-121157	19971022
CZ 291768	B6	CZ 1997-3106	19971001
PH 1199758268	B1	PH 1997-58268	19971022
HU 222540	B1	HU 1997-1660	19971017

FILING DETAILS:

PATENT NO	KIND		PATENT NO
NO 308362	B1	Previous Publ.	NO 9704934
AU 726092	B	Previous Publ.	AU 9742788
DE 59705964	G	Based on	EP 838469
ES 2170318	T3	Based on	EP 838469
SK 283114	B6	Previous Publ.	SK 9701419
CZ 291768	B6	Previous Publ.	CZ 9703106

PRIORITY APPLN. INFO: DE 1996-19644195 19961024

AN 1998-232593 [21] WPIDS

AB EP 838469 A UPAB: 19980528

[(1'R),2R,3S,4S,5R,6R,9R,11R,12R,14R]-11-(1'-hydroxypropyl)-2,4,6,8,11,14-hexamethyl-10,13,15-trioxatricyclo[9.2.1.19.6]pentadecan-1-one derivatives of formula (I) and their salts are new: R1 = H or Me.

USE - (I) are erythromycin A derivatives, useful as motilin agonists to increase gastro-intestinal tone and motility in conditions such as dyspepsia, gastro-intestinal reflux and post-operative gastro-intestinal motility disorders.

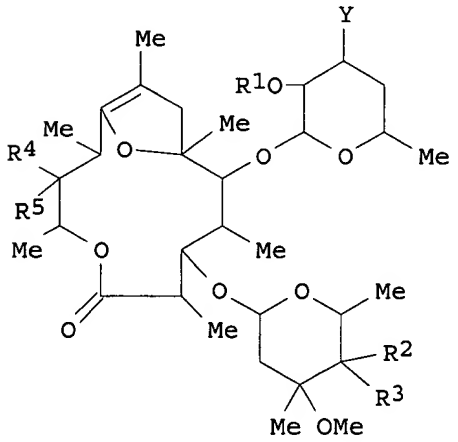
ADVANTAGE - (I) are erythromycin A derivatives, but do not have its antibiotic activity and the associated side effects (e.g. gastrointestinal contraction). They have good oral bioavailability and activity profiles and have high selectivity for **motilin receptors.**

Dwg.0/0

L19 ANSWER 160 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:388532 CAPLUS
DOCUMENT NUMBER: 129:41373
TITLE: Preparation of 13-membered ring macrolide compounds as digestive tract contraction promoters
INVENTOR(S): Ataka, Kikuo; Miyata, Hiroyuki; Takama, Akira
PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan; Ataka, Kikuo; Miyata, Hiroyuki; Takama, Akira
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9823629	A1	19980604	WO 1997-JP4277	19971125
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
JP 10212295	A2	19980811	JP 1997-316880	19971118
AU 9749689	A1	19980622	AU 1997-49689	19971125
US 6100239	A	20000808	US 1999-308879	19990525

PRIORITY APPLN. INFO.: JP 1996-314526 A 19961126
WO 1997-JP4277 W 19971125
OTHER SOURCE(S): CASREACT 129:41373; MARPAT 129:41373
GI



I

AB The title compds. I [R1 and R2 each represents hydrogen and R3 represents hydrogen, hydroxy, or amino, provided that R2 and R3 in combination may represent oxo, etc.; R4 and R5 in combination represent oxo; and Y represents N(R6)(R7) or N+(R8)(R9)(R10) X-, where R6 to R10 each represents hydrogen, lower alkyl, etc., and X- represents an anion] are prepared In an in vitro test for the inhibition of motilin binding to the **motilin receptor**, I [R1 = H; R2 = H; R3 = OH; Y = NMe2; R4R5 = oxo] showed IC50 of 5.7 x 10-9 M.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 161 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:87750 CAPLUS
DOCUMENT NUMBER: 128:145337
TITLE: Isolation of 15-hydroxy-8,9-anhydroerythromycin derivatives from rat urine as metabolites of erythromycin derivatives
INVENTOR(S): Ishitani, Yoshihiko; Takata, Shotaro; Ishigai, Masaki; Nishigoori, Yoshiko
PATENT ASSIGNEE(S): Chugai Seiyaku K. K., Japan; Ishitani, Yoshihiko; Takata, Shotaro; Ishigai, Masaki; Nishigoori, Yoshiko
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9803531	A1	19980129	WO 1997-JP2554	19970724
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9736343	A1	19980210	AU 1997-36343	19970724
JP 10087686	A2	19980407	JP 1997-198316	19970724

PRIORITY APPLN. INFO.: JP 1996-225806 19960724
WO 1997-JP2554 19970724
OTHER SOURCE(S): MARPAT 128:145337
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. represented by general formula [I; R1 = hydrogen or acyl; R2, R3 = hydrogen, hydroxy, acyloxy or amino, or R2 and R3 may form together :O or :NOR12 (wherein R12 = hydrogen or lower alkyl); R4 = hydrogen or lower alkyl; R5, R6 = hydrogen or hydroxy, provided that at least one of them is hydroxy; Y = NR7R8 or N+R9R10R11X1 (wherein R7 - R11 = hydrogen, lower alkyl, lower alkenyl, cycloalkyl, etc., or R7 and R8, or R9 and R10 may, together with the adjacent nitrogen, form each azacyclo-alkyl); X- = an anion] or pharmaceutically acceptable salts thereof, which are useful as drugs for promoting the digestive tract motions, etc., are obtained from rat urine as metabolites of erythromycin derivs. Thus, a 8,9-anhydroerythromycin A-6,9-hemiketal derivative (II; R = H) was administered p.o. to rats followed by extraction of urine and HPLC purification to give II (R = OH) which inhibited the binding of motilin to **motilin receptor** preparation from homogenized rabbit upper small intestine with IC50 value of 10+10-9 M compared to 19+10-9 M for I (R = H).
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 162 OF 391 MEDLINE on STN DUPLICATE 74
ACCESSION NUMBER: 1998387868 MEDLINE
DOCUMENT NUMBER: 98387868 PubMed ID: 9719592
TITLE: Synthesis of 9-deoxo-4''-deoxy-6,9-epoxyerythromycin derivatives: novel and acid-stable motilides.
AUTHOR: Faghih R; Lartey P A; Nellans H N; Seif L; Burnell-Curty C; Klein L L; Thomas P; Petersen A; Borre A; Pagano T; Kim K H; Heindel M; Bennani Y L; Plattner J J

CORPORATE SOURCE: Pharmaceutical Discovery Division, Abbott Laboratories, Abbott Park, Illinois 60064-3500, USA.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1998 Aug 27) 41 (18) 3402-8.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980917

AB In our quest toward the discovery of highly potent and acid-stable motilides, novel 4"-deoxy derivatives of 9-deoxo-6, 9-epoxyerythromycin were designed, synthesized, and evaluated for their gastrointestinal prokinetic activities. These compounds, in their 9R configuration, were more potent than their 6,9-enol ether homologues in inducing well-coordinated smooth muscle contractions in an in vitro rabbit duodenal assay: e.g., (9R), (8S)-9-deoxo-4"-deoxy-3'-N-desmethyl-3'-N-ethyl-6, 9-epoxyerythromycin A (10) and (9R), (8S)-9-deoxo-4"-deoxy-3'-N-desmethyl-3'-N-ethanol-6, 9-epoxyerythromycin A (15) had a pED50 of 8.54 and 8.11 compared to a pED50 of 7.22 for compound 2 (ABT-229). Reduction of the 6,9-enol ether, which was aimed at improving the acid stability, afforded the most stable motilides to date with t1/2 of 5.5 h for 10 and 15. Compounds 10 and 15 bind specifically to rabbit antral smooth muscle **motilin receptors** with pIC50 values of 8.52 and 8.70.

L19 ANSWER 163 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:468265 BIOSIS
DOCUMENT NUMBER: PREV199800468265
TITLE: **Motilin receptors** in the human GI tract.
AUTHOR(S): Miller, P.; Roy, A.; Dagenais, M.; Lapointe, R.; St-Pierre, S.; Poitras, P.
CORPORATE SOURCE: CHUM-Saint Luc, Montreal, Canada
SOURCE: Digestive Diseases and Sciences, (Aug., 1998) Vol. 43, No. 8, pp. 1888. print.
Meeting Info.: 12th International Symposium on Regulatory Peptides. Mackinac Island, Michigan, USA. September 16-20, 1998.
CODEN: DDSCDJ. ISSN: 0163-2116.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 1998
Last Updated on STN: 30 Oct 1998

L19 ANSWER 164 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:468143 BIOSIS
DOCUMENT NUMBER: PREV199800468143
TITLE: Regulation of motilin and of **motilin receptors** during TNBS-colitis in rabbits.
AUTHOR(S): Depoortere, I.; Van Assche, G.; Peeters, T. L.
CORPORATE SOURCE: Gut Hormone Lab., Univ. Leuven, Leuven B-3000, Belgium
SOURCE: Digestive Diseases and Sciences, (Aug., 1998) Vol. 43, No. 8, pp. 1857. print.
Meeting Info.: 12th International Symposium on Regulatory Peptides. Mackinac Island, Michigan, USA. September 16-20, 1998.
CODEN: DDSCDJ. ISSN: 0163-2116.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 1998

Last Updated on STN: 30 Oct 1998

L19 ANSWER 165 OF 391 MEDLINE on STN DUPLICATE 75
ACCESSION NUMBER: 1999094689 MEDLINE
DOCUMENT NUMBER: 99094689 PubMed ID: 9880080
TITLE: Anxiolytic effect of motilin and reversal with GM-109, a motilin antagonist, in mice.
AUTHOR: Momose K; Inui A; Asakawa A; Ueno N; Nakajima M; Kasuga M
CORPORATE SOURCE: Second Department of Internal Medicine, Kobe University School of Medicine, Japan.
SOURCE: PEPTIDES, (1998) 19 (10) 1739-42.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990615

AB There have been few reports on the effects of the brain-gut peptide motilin on the central nervous system (CNS). We administered motilin intracerebroventricularly to mice and investigated the effect of motilin on anxiety using an elevated plus-maze. Motilin produced a significant decrease in anxiety with an inverted U-shaped dose response. To determine whether the anxiolytic effect of motilin was mediated via **motilin receptors** in the brain, the effect of GM-109, a novel **motilin receptor** antagonist, was investigated. GM-109 showed a significant and dose-dependent antagonism on the motilin-induced anxiolytic effect. GM-109 administered alone had no effect on anxiety. These results suggest that **motilin receptors** are present in the brain and may have a role in anxiety and emotion.

L19 ANSWER 166 OF 391 MEDLINE on STN DUPLICATE 76
ACCESSION NUMBER: 1998389546 MEDLINE
DOCUMENT NUMBER: 98389546 PubMed ID: 9724153
TITLE: Cephalosporin antibiotics accelerate gastric emptying in mice.
AUTHOR: Kuo W H; Wadwa K S; Ferris C D
CORPORATE SOURCE: Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (1998 Aug) 43 (8) 1690-4.
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980916

AB Gastroparesis is a common debilitating complication in many diabetic patients. While several drugs are available for gastroparesis, many patients are not adequately treated. Many patients do not respond to available drugs or appear to develop tachyphylaxis after an initial response. New agents are needed. Erythromycin is a macrolide antibiotic that accelerates gastric emptying through interaction with **motilin receptors.** Many antibiotics, like erythromycin itself, have significant gastrointestinal side effects. We investigated the ability of cephalosporin antibiotics to alter gastric emptying in mice by employing phenol red spectrophotometry to monitor gastric emptying. Our results indicate that several cephalosporin antibiotics, particularly cefazolin, accelerate gastric emptying. In some cases these drugs appear more efficacious than either erythromycin or metoclopramide. At very high doses, many drugs, including erythromycin, appear to delay gastric

emptying. We hypothesize that the gastrointestinal side effects of nausea and vomiting may result from delayed gastric emptying occurring at high doses while lower doses are prokinetic in the stomach.

L19 ANSWER 167 OF 391 MEDLINE on STN DUPLICATE 77
ACCESSION NUMBER: 1999256764 MEDLINE
DOCUMENT NUMBER: 99256764 PubMed ID: 10326832
TITLE: Hypotensive mechanism of [Leu13]motilin in dogs in vivo and in vitro.
AUTHOR: Iwai T; Nakamura H; Takanashi H; Yogo K; Ozaki K; Ishizuka N; Asano T
CORPORATE SOURCE: Chugai Pharmaceutical Co. Ltd., Fuji-Gotemba Research Labs, Shizuoka, Japan.. iwaitks@gt.chugai-pharm.co.jp
SOURCE: CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1998 Dec) 76 (12) 1103-9.
Journal code: 0372712. ISSN: 0008-4212.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990714
Last Updated on STN: 19990714
Entered Medline: 19990630
AB The effects of [Leu13]motilin were examined in vivo after its intravenous administration into anesthetized dogs and in vitro with isolated preparations of canine mesenteric artery. [Leu13]Motilin (0.1-10 nmol x kg(-1), i.v.) induced both strong and clustered phasic contractions in the gastric antrum and duodenum. At doses of over 1 nmol x kg(-1), [Leu13]motilin also produced transient decreases in arterial blood pressure, left ventricular pressure, maximum rate of rise of left ventricular pressure, and total peripheral resistance, and an increase in aortic blood flow and heart rate. A selective motilin antagonist, GM-109 (Phe-cyclo[Lys-Tyr(3-tBu)-betaAla] trifluoroacetate), completely abolished the gastric antrum and duodenal motor responses induced by [Leu13]motilin. In contrast, hypotension induced by [Leu13]motilin (1 nmol x kg(-1)) was unchanged in the presence of GM-109. In isolated mesenteric artery preparations precontracted with U-46619 (10(-7) M), [Leu13]motilin (10(-8)-10(-5) M) induced an endothelium-dependent relaxation, and this was inhibited by a pretreatment with N(omega)-nitro-L-arginine, a competitive inhibitor of NO synthase (10(-4) M). A high dose (10(-4) M) of GM-109 slightly decreased [Leu13]motilin-induced relaxation, and shifted the concentration-response curve of [Leu13]motilin to the right. However, the pA2 value (4.09) of GM-109 for [Leu13]motilin in the present study was conspicuously lower than that previously demonstrated in the rabbit duodenum (7.37). These results suggest that [Leu13]motilin induces hypotension via the endothelial NO-dependent relaxation mechanism and not through the receptor type that causes upper gastrointestinal contractions.

L19 ANSWER 168 OF 391 MEDLINE on STN DUPLICATE 78
ACCESSION NUMBER: 1998366102 MEDLINE
DOCUMENT NUMBER: 98366102 PubMed ID: 9700745
TITLE: Motilin increases food intake in mice.
AUTHOR: Asakawa A; Inui A; Momose K; Ueno N; Fujino M A; Kasuga M
CORPORATE SOURCE: Second Department of Internal Medicine, Kobe University School of Medicine, Japan.
SOURCE: PEPTIDES, (1998) 19 (6) 987-90.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106

Entered Medline: 19981023

AB The effect of motilin on food intake was investigated in nonfood-deprived mice. A significant increase in food intake was observed 1 h after ICV administration of motilin (3 nmol/mouse) and continued for 2 h. This effect was attenuated markedly by the **motilin receptor** antagonist GM-109 (0.3-3 nmol/mouse) in a dose-related manner. GM-109 alone had no effect on food intake. These results indicate that **motilin receptors** are present in the brain and may have a role in the regulation of food intake.

L19 ANSWER 169 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 79

ACCESSION NUMBER: 1999:25355 BIOSIS
DOCUMENT NUMBER: PREV199900025355
TITLE: Motilides and motilactides: Design and development of **motilin receptor** agonists as a new class of gastrointestinal prokinetic drugs.
AUTHOR(S): Faghih, Ramin [Reprint author]; Nellans, Hugh N.; Plattner, Jacob J.
CORPORATE SOURCE: Pharm. Discovery Div., Abbott Lab., 100 Abbott Park Rd., Abbott Park, IL 60064-3500, USA
SOURCE: Drugs of the Future, (Aug., 1998) Vol. 23, No. 8, pp. 861-872. print.
ISSN: 0377-8282.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jan 1999
Last Updated on STN: 20 Jan 1999

L19 ANSWER 170 OF 391 MEDLINE on STN DUPLICATE 80

ACCESSION NUMBER: 1998356951 MEDLINE
DOCUMENT NUMBER: 98356951 PubMed ID: 9691922
TITLE: Motilin induces gall bladder emptying and antral contractions in the fasted state in humans.
AUTHOR: Luiking Y C; Peeters T L; Stolk M F; Nieuwenhuijs V B; Portincasa P; Depoortere I; van Berge Henegouwen G P; Akkermans L M
CORPORATE SOURCE: Department of Surgery, University Hospital Utrecht, The Netherlands.
SOURCE: GUT, (1998 Jun) 42 (6) 830-5.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980814

AB BACKGROUND: Animal studies have shown that motilin affects gall bladder motility. In humans, no effect has been shown, but erythromycin, a **motilin receptor** agonist, induces gall bladder emptying.
AIMS: To explore the effect of increasing doses of exogenous motilin on gall bladder volume and antral contractility in the fasted state in humans. METHODS: After an overnight fast, eight healthy men received increasing intravenous doses of Leu13-motilin (KW-5139) or 0.9% NaCl in a double blind, randomised fashion. Gall bladder volume and antral contraction frequency were determined by ultrasonography. RESULTS: Infusion of motilin increased plasma motilin levels. Motilin induced a reduction in gall bladder volume of 8.0 (5.0)%, 17.1 (5.0)%, 18.5 (4.7)%, and 16.1 (4.9)% of baseline volume at the end of infusion of 2, 4, 8, and 16 pmol/kg/min respectively, compared with mean stable gall bladder

volumes during placebo infusion ($p < 0.05$). Antral contraction frequency increased during motilin infusion, but not during placebo infusion ($p < 0.05$). CONCLUSIONS: Exogenous motilin reducted fasting gall bladder volume and increased antral contractions. After reaching maximal reduction, the gall bladder volume did not decrease further during continuous motilin infusion at higher doses and stayed at the same reduced volume. The degree of gall bladder volume reduction during motilin infusion mimicked gall bladder emptying preceding antral phase III activity of the migrating motor complex in humans. This study indicates that motilin may play a physiological role in the regulation of gall bladder emptying in the fasted state.

L19 ANSWER 171 OF 391 MEDLINE on STN
ACCESSION NUMBER: 1999088711 MEDLINE
DOCUMENT NUMBER: 99088711 PubMed ID: 9871545
TITLE: Preparation of 9-deoxo-4"-deoxy-6,9-epoxyerythromycin lactams "motilactides": potent and orally active prokinetic agents.
AUTHOR: Faghih R; Nellans H N; Lartey P A; Petersen A; Marsh K; Bennani Y L; Plattner J J
CORPORATE SOURCE: Pharmaceutical Discovery Division, Abbott Laboratories, Abbott Park, IL 60064, USA.
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (1998 Apr 7) 8 (7) 805-10.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990127
AB A series of new, highly potent and orally active "motilactides", 9-deoxo-4"-deoxy-6,9-epoxyerythromycin lactams was designed, synthesized, and evaluated for their gastrointestinal motor stimulating activity. These compounds were acid stable and showed good oral efficacy.

L19 ANSWER 172 OF 391 MEDLINE on STN DUPLICATE 81
ACCESSION NUMBER: 1999026197 MEDLINE
DOCUMENT NUMBER: 99026197 PubMed ID: 9808701
TITLE: Effects of EM574 and cisapride on gastric contractile and emptying activity in normal and drug-induced gastroparesis in dogs.
AUTHOR: Tanaka T; Mizumoto A; Mochiki E; Suzuki H; Itoh Z; Omura S
CORPORATE SOURCE: Gastrointestinal Research Laboratory, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Japan.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 Nov) 287 (2) 712-9.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981207
AB EM574, an erythromycin derivative and potent **motilin receptor** agonist, is now undergoing clinical trials as a gastroprokinetic drug. The aim of this study was to compare the effect of EM574 with that of cisapride on gastric motility and emptying in normal and gastroparesis dogs. Six dogs were each implanted with two duodenal cannulas for infusion of phenolsulfonphthalein into the proximal duodenum

and for aspiration of luminal samples from the distal duodenum. Both solid and liquid gastric emptying were determined by a novel freeze-drying method developed in our laboratory. A freeze-dried standard meal (100 g, 400 kcal) was given with 100 ml normal saline containing 15 g of polyethylene glycol as a liquid marker. Gastric muscle contractility was measured by means of a force transducer implanted on the gastric antrum. EM574 (3-30 microgram/kg) and cisapride (0.3-3.0 mg/kg) were administered intraduodenally at the start of feeding. Clonidine (3-30 microgram/kg) was injected subcutaneously 15 min before feeding to induce gastroparesis. EM574 and cisapride both enhanced gastric muscle contractility in a dose-dependent manner. EM574 (30 microgram/kg and 10 microgram/kg) significantly accelerated gastric emptying of solids and liquids, respectively. Cisapride (1 mg/kg) significantly accelerated solid gastric emptying, but 3.0 mg/kg significantly delayed liquid gastric emptying. Clonidine (10 and 30 microgram/kg) significantly delayed solid and liquid gastric emptying and reduced gastric muscle contractility. EM574, at a dose of 30 microgram/kg, completely restored solid and liquid gastric emptying and muscle contractility to the normal range in dogs with clonidine-induced gastroparesis. Cisapride (1 mg/kg) restored liquid gastric emptying in dogs with gastroparesis to the normal range and partially restored solid emptying. EM574 accelerated gastric muscle contractility and emptying of solids and liquids in normal dogs. The stimulating activity of EM574 on gastric muscle contractility and emptying was comparable to that of cisapride, but EM574 was as effective as cisapride in normalizing gastric muscle contractility and emptying in dogs with clonidine-induced gastroparesis.

L19 ANSWER 173 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:669282 CAPLUS
DOCUMENT NUMBER: 130:108217
TITLE: The changes in the gastric motility in patients with gastritis, gastric ulcer or gastric cancer
AUTHOR(S): Tamura, Tatsuya; Kusano, Motoyasu
CORPORATE SOURCE: Medical School, Gunma University, Japan
SOURCE: Igaku no Ayumi (1998), 186(9), 557-561
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 16 refs., on changes gastrointestinal motility in gastritis, gastric ulcer, and gastric cancer. The involvement of motilin, **motilin receptor**-regulating agents, and gastrin in gastric motility and gastric diseases is also discussed.

L19 ANSWER 174 OF 391 MEDLINE on STN DUPLICATE 82
ACCESSION NUMBER: 1998191180 MEDLINE
DOCUMENT NUMBER: 98191180 PubMed ID: 9530149
TITLE: Postsynaptic enhancement by motilin of muscarinic receptor cation currents in duodenal smooth muscle.
AUTHOR: Yamada K; Yanagida H; Ito Y; Inoue R
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1998 Mar) 274 (3 Pt 1) G487-92.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980507
Last Updated on STN: 19980507
Entered Medline: 19980424
AB We have investigated a potential role of motilin in amplifying the postsynaptic muscarinic responses in the rabbit duodenal smooth muscle

cells, using the whole cell variant of patch-clamp technique. Stimulation of **motilin receptors** by exogenously applied motilin (1 nM) resulted in a large increase in carbachol (CCh)-induced atropine-sensitive cation current (ICCh) at threshold concentrations of CCh (0.3-1 microM) at 30 degrees C. This potentiation was abolished in the presence of a specific blocker of **motilin receptor** (GM109) and was attenuated with increased concentrations of either motilin or CCh, being virtually absent with maximally effective concentrations of these agonists. Motilin failed to potentiate ICCh when the ambient temperature was reduced to 20 degrees C or if the cation current had been directly activated by internal perfusion with guanosine 5'-O-(3-thiotriphosphate) (50 microM) bypassing the muscarinic receptor. These results suggest that some biochemical processes, such as enzymatic reactions, might be involved in the motilin-induced potentiation and that its site of action might be the muscarinic receptor and/or associated G proteins.

L19 ANSWER 175 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:208926 SCISEARCH
THE GENUINE ARTICLE: ZA599
TITLE: Postsynaptic enhancement by motilin of muscarinic receptor cation currents in duodenal smooth muscle
AUTHOR: Yamada K; Yanagida H; Ito Y; Inoue R (Reprint)
CORPORATE SOURCE: KYUSHU UNIV, FAC MED, DEPT PHARMACOL, FUKUOKA 81282, JAPAN (Reprint); KYUSHU UNIV, FAC MED, DEPT PHARMACOL, FUKUOKA 81282, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (MAR 1998) Vol. 37, No. 3, pp. G487-G492. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0193-1857.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have investigated a potential role of motilin in amplifying the postsynaptic muscarinic responses in the rabbit duodenal smooth muscle cells, using the whole cell variant of patch-clamp technique. Stimulation of **motilin receptors** by exogenously applied motilin (1 nM) resulted in a large increase in carbachol (CCh)-induced atropine-sensitive cation current (I-CCh) at threshold concentrations of CCh (0.3-1 mu M) at 30 degrees C. This potentiation was abolished in the presence of a specific blocker of **motilin receptor** (GM109) and was attenuated with increased concentrations of either motilin or CCh, being virtually absent with maximally effective concentrations of these agonists. Motilin failed to potentiate I-CCh when the ambient temperature was reduced to 20 degrees C or if the cation current had been directly activated by internal perfusion with guanosine 5'-O-(3-thiotriphosphate) (50 mu M) bypassing the muscarinic receptor. These results suggest that some biochemical processes, such as enzymatic reactions, might be involved in the motilin-induced potentiation and that its site of action might be the muscarinic receptor and/or associated G proteins.

L19 ANSWER 176 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:673152 SCISEARCH
THE GENUINE ARTICLE: 115AY
TITLE: Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans
AUTHOR: Coulie B; Tack J (Reprint); Peeters T; Janssens J
CORPORATE SOURCE: CATHOLIC UNIV LOUVAIN, UNIV HOSP GASTHUISBERG, DEPT INTERNAL MED, DIV GASTROENTEROL, HERESTR 49, B-3000 LOUVAIN, BELGIUM (Reprint); CATHOLIC UNIV LOUVAIN, UNIV

HOSP GASTHUISBERG, DEPT INTERNAL MED, DIV GASTROENTEROL, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GUT, (SEP 1998) Vol. 43, No. 3, pp. 395-400. Publisher: BRITISH MED JOURNAL PUBL GROUP, BRITISH MED ASSOC HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR, ENGLAND. ISSN: 0017-5749.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 29
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background - During the interdigestive state in humans, erythromycin 40 mg induces a premature activity front that starts in the stomach, while erythromycin 200 mg induces a prolonged period of enhanced antral contractile activity.

Aims - To study the involvement of a cholinergic pathway in the motor effects of erythromycin using the muscarinic antagonist atropine and the neural 5-HT1 receptor agonist sumatriptan.

Methods - In 30 healthy volunteers, fasted antroduodenojejunal motor activity was studied by stationary manometry. Placebo (n = 10), atropine (15 mu g/kg intravenous bolus plus 15 mu g/kg/h over 30 minutes; n = 10), or sumatriptan (6 mg subcutaneously; n = 10) was administered, followed by infusion of erythromycin 40 mg or 200 mg.

Results - After placebo, erythromycin 40 mg induced a premature activity front with gastric onset after 19.1 (1.7) minutes in all volunteers. After atropine, erythromycin 40 mg failed to induce a premature activity front during a 60 minute period in all volunteers ($p < 0.001$), while sumatriptan prevented the induction of a premature activity front during a 60 minute period in all but one volunteer ($p < 0.005$). The number of antral contractions and their mean amplitude in the 60 minutes after erythromycin 200 mg did not differ significantly after atropine or sumatriptan versus placebo.

Conclusions - The antral motor effects of erythromycin in humans are mediated via different pathways. The induction of a premature activity front is mediated through activation of an intrinsic cholinergic pathway, while the induction of enhanced antral contractile activity may be mediated via a pathway potentially involving activation of a muscular receptor.

L19 ANSWER 177 OF 391 MEDLINE on STN DUPLICATE 83
ACCESSION NUMBER: 1998353038 MEDLINE
DOCUMENT NUMBER: 98353038 PubMed ID: 9690728
TITLE: Which form of erythromycin should be used to treat gastroparesis? A pharmacokinetic analysis.
AUTHOR: Ehrenpreis E D; Zaitman D; Nellans H
CORPORATE SOURCE: Department of Gastroenterology, University of Chicago, Illinois 60637, USA.
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1998 Apr) 12 (4) 373-6. Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981014

AB BACKGROUND: Erythromycin is a macrolide antibiotic that exhibits prokinetic effects. It has been shown to enhance antral contractility and accelerates gastric emptying rates, primarily by stimulating **motilin receptors.** AIM: To determine the optimal dosage form of erythromycin for use as a prokinetic agent. METHODS: Eight normal volunteers and three patients with documented gastroparesis ingested 250

mg erythromycin in tablet. suspension and intravenous forms. Serum erythromycin levels were determined at frequent intervals. These data were plotted vs. time and analysed for lag time, time to maximum concentration (tmax), maximum concentration (Cmax) and bioavailability (F). RESULTS: The absorption kinetics of the erythromycin suspension was notable for short lag times and early tmax, while lag times and tmax were delayed with the tablet form. Median lag time was 15 min for the suspension vs. 90 min for the tablet ($P < 0.005$). Median tmax for the suspension was 45 min vs. 180 min for the tablet ($P < 0.005$). A non-significant decrease in F was seen with the suspension compared to the tablet ($P = 0.12$). CONCLUSION: Based on the kinetic data from this study, erythromycin suspension is the ideal dosage form for administration of this drug as a prokinetic agent.

L19 ANSWER 178 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:427097 SCISEARCH
THE GENUINE ARTICLE: ZQ581
TITLE: Effect of erythromycin lactobionate on myoelectric activity of ileum, cecum, and right ventral colon, and cecal emptying of radiolabeled markers in clinically normal ponies
AUTHOR: Lester G D (Reprint); Merritt A M; Neuwirth L; VetroWidenhouse T; Steible C; Rice B
CORPORATE SOURCE: UNIV FLORIDA, COLL VET MED, DEPT LARGE ANIM CLIN SCI, GAINESVILLE, FL 32610 (Reprint); UNIV FLORIDA, COLL VET MED, DEPT SMALL ANIM CLIN SCI, GAINESVILLE, FL 32610; UNIV FLORIDA, DEPT STAT, GAINESVILLE, FL 32610
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF VETERINARY RESEARCH, (MAR 1998) Vol. 59, No. 3, pp. 328-334.
Publisher: AMER VETERINARY MEDICAL ASSOC, 1931 N MEACHAM RD SUITE 100, SCHAUMBURG, IL 60173-4360.
ISSN: 0002-9645.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: AGRI
LANGUAGE: English
REFERENCE COUNT: 29

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective-To determine the effect of erythromycin lactobionate (ERY) on ileocecocolic myoelectric activity and passage of radiolabeled markers from the cecum.

Animals-6 healthy adult ponies.

Procedure-After a 12-hour nonfeeding period, 370 MBq of technetium 99m-labeled sulfur colloid in egg albumen and 37 MBq of indium 111-labeled diethyitriaminepentaacetic acid in 60 mi of water were administered directly into the cecal apex. The following drug concentrations were tested: ERY, 0.01,0.10, 1.0, and 10.0 mg/kg of body weight; ERY, 0.10 mg/kg bolus; and saline (0.9% NaCl) solution, 10 ml. All treatments with the exception of the 0.10-mg/kg bolus and saline solution, were infusions administered IV during a 60-minute period in a randomized complete block design. Each treatment was administered 2 times/pony. Dual-phase scintigraphic images were obtained, and the best-fit function was determined for each study, using data from the right side. Myoelectric data were collected before and after each treatment and analyzed for spike burst rate, relative activity, and burst duration.

Results-The time to 50% emptying (t(50)) after ERY administration was dose dependent, and all treatments, with the exception of the 0.01-mg/kg infusion, resulted in a significantly shorter t(50) than that observed after saline administration (230.2 +/- 17.12 minutes). The shortest t(50) was observed after the 1.0 mg/kg dosage of ERY (76.9 +/- 22.0 minutes). Although not significantly different, the t(50) and beta were shorter (108.6 +/- 25.9 minutes) and steeper after a bolus dose of 0.10 mg/kg of ERY than after infusion at the same dosage (131.1 +/- 18.7 minutes).

Conclusions and Clinical Relevance-ERY may be a useful prokinetic for prevention or treatment of cecal motility dysfunction. The ability of ERY

to evoke a similar response during the early postanesthetic or postoperative period remains to be determined.

L19 ANSWER 179 OF 391 MEDLINE on STN DUPLICATE 84
ACCESSION NUMBER: 1999049151 MEDLINE
DOCUMENT NUMBER: 99049151 PubMed ID: 9832311
TITLE: Identification of the motilide pharmacophores using quantitative structure activity relationships.
AUTHOR: Khiat A; Boulanger Y
CORPORATE SOURCE: Departement de radiologie, Centre Hospitalier de l'Universite de Montreal, Quebec, Canada.
SOURCE: JOURNAL OF PEPTIDE RESEARCH, (1998 Oct) 52 (4) 321-8. Journal code: 9707067. ISSN: 1397-002X.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990127

AB Erythromycin A and some derivatives have been shown to act as agonists at the **motilin receptor** site (motilides) and a structural similarity between these molecules and the N-terminal fragment of motilin has been proposed. Conformational analysis and three-dimensional quantitative structure-activity relationship (3D-QSAR) methods have been used to determine the homology between a series of erythromycin A derivatives and motilin 1-10. A total of 18 compounds has been studied to correlate the gastrointestinal motor stimulating (GMS) activity with the structure-related parameters determined by 3D-QSAR. Two models with good predictive power of the GMS activity are presented, leading to the prediction of motilin 1-10 activity. The models are consistent with the majority of the data available. The most significant parameters for GMS activity are a favorable dispersion interaction from the quaternary ammonium group of the desosamine ring. In motilin 1-10, the aromatic side chains of Phe1 and Tyr7 seem to play the same role as the quaternary ammonium group in models 1 and 2, respectively. Some hydroxyl groups of erythromycin A derivatives and hydrophobic groups of the Val2 and Ile4 side chains of motilin also contribute to the GMS activity. The experimental GMS activities measured are in good agreement with the predicted values, with correlation coefficient values of 0.98 and 0.94 in models 1 and 2, respectively.

L19 ANSWER 180 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:302788 CAPLUS
DOCUMENT NUMBER: 129:103755
TITLE: Chemistry and SAR of prokinetic motilides: non-peptidic **motilin receptor** agonists
AUTHOR(S): Lartey, P. A.
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Pharmacochemistry Library (1998), 29(Trends in Drug Research II), 167-178
CODEN: PHLIDQ; ISSN: 0165-7208
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Compds. derived from erythromycin with improved prokinetic action but no antibacterial activity, dubbed motilides, will be useful as drugs for the treatment of gastrointestinal motility disorders. The discovery, chemical, and SAR of the motilide class of prokinetic agents are discussed.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 181 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:257316 CAPLUS
DOCUMENT NUMBER: 129:42
TITLE: Effect of motilide on gastrointestinal motility with special reference to diabetic gastroparesis
AUTHOR(S): Asakawa, Akihiro; Inui, Akio
CORPORATE SOURCE: Second Dep. Intern. Med., Kobe Univ. Sch. Med., Japan
SOURCE: Cell (Tokyo) (1998), 30(3), 90-93
CODEN: SAIBD8; ISSN: 0386-4766
PUBLISHER: Nyu Saiensusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 11 refs., of the chemical, effect on gastrointestinal motility, and clin. pharmacol. of motilides (acting at motin receptors e.g. EM523) for treatment of diabetic gastroparesis.

L19 ANSWER 182 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:693050 CAPLUS
DOCUMENT NUMBER: 130:20827
TITLE: Localization of motilin binding sites in subcellular fractions from rabbit antral and colonic smooth muscle tissue
AUTHOR(S): Van Assche, Gert; Depoortere, Inge; Peeters, Theo L.
CORPORATE SOURCE: Gut Hormone Laboratory, University of Leuven, Louvain, B-3000, Belg.
SOURCE: Regulatory Peptides (1998), 77(1-3), 89-94
CODEN: REPPDY; ISSN: 0167-0115
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Motilin stimulates gastrointestinal motility, but in vitro studies reveal a direct smooth muscle effect, whereas in vivo studies reveal a neurally mediated effect. The aim of the present study was to determine if motilin binds to microsomes (smooth muscle) and/or synaptosomes (neurons). Subcellular fractions were prepared from tissue of rabbit gastric antrum and colon by differential centrifugation and d. gradient centrifugation and characterized by determining motilin binding and the presence of membrane markers. The purified microsomal fraction, enriched in the smooth muscle marker 5'-nucleotidase, was found to have the highest specific motilin binding in both antrum and colon. In the antrum, but not in the colon, the mitochondrial fraction also showed enrichment of [3H]-saxitoxin binding (marker for synaptosomes) and motilin binding, although the latter was much lower than in the microsomal fraction. Two receptor binding sites were characterized in both the antral mitochondrial/synaptosomal and colonic microsomal fraction (antrum: pKd,1 9.89, pKd,2 8.18, colon: pKd,1 9.72, pKd,2 8.39). Thus, motilin binding is predominantly associated with smooth muscle membranes in both antrum and colon of the rabbit. In both organs two motilin binding sites are present with comparable affinities, but the d. in the colon is much higher for both sites. Whether they represent neural and smooth muscle receptors will require studies with isolated smooth muscle cells and neurons.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 183 OF 391 JAPIO (C) 2004 JPO on STN FAMILY 85
ACCESSION NUMBER: 1997-249620 JAPIO
TITLE: ARYLALKANE DERIVATIVE
INVENTOR: SUZUKI MASATOSHI; OUCHI YUTAKA
PATENT ASSIGNEE(S): TAISHO PHARMACEUT CO LTD
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 09249620	A	19970922	Heisei	C07C211-40

APPLICATION INFORMATION

STN FORMAT:	JP 1996-56167	19960313
ORIGINAL:	JP08056167	Heisei

PRIORITY APPLN. INFO.: JP 1996-56167 19960313
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 1997

AN 1997-249620 JAPIO

AB PROBLEM TO BE SOLVED: To obtain a new arylalkane derivative having a stimulating action on a **motilin receptor**, exhibiting activating action on enterokinesis, effective for treating gastrointestinal diseases followed by enterokinesis insufficiency. SOLUTION: This arylalkane derivative is shown by formula I ((n) is an integer of 1 to 4; A is a benzene ring, etc.; R<SP>1</SP> and R<SP>2</SP> are each H, H, a 1-3C alkyl, etc.; X is CH or N; D is a halogen, etc.) such as N,N-dimethyl-4-(3,5- diphenyl-3-pentenyl)aniline. The compound of formula I in which D is CH is obtained by condensing a compound of formula II with a compound of formula III.

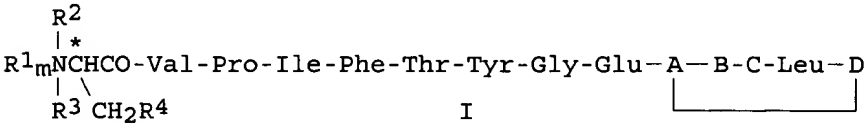
L19 ANSWER 184 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1997:761836 CAPLUS
DOCUMENT NUMBER:	127:359107
TITLE:	Preparation of motilin-like cyclopeptides with gastrointestinal motor stimulating activity
INVENTOR(S):	Dharanipragada, Ramalinga; Macielag, Mark J.; Kim-Dettelback, Jung; Florance, James
PATENT ASSIGNEE(S):	Ohmeda Pharmaceutical Products Division Inc., USA
SOURCE:	Eur. Pat. Appl., 25 pp. CODEN: EPXXDW
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 807639	A2	19971119	EP 1997-303251	19970513
EP 807639	A3	19971126		
EP 807639	B1	20000209		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE, IE				
US 5734012	A	19980331	US 1996-648644	19960516
CA 2200935	AA	19971116	CA 1997-2200935	19970325
ES 2144826	T3	20000616	ES 1997-303251	19970513
JP 10053599	A2	19980224	JP 1997-126736	19970516

PRIORITY APPLN. INFO.: US 1996-648644 A 19960516
OTHER SOURCE(S): MARPAT 127:359107
GI



I

AB This invention pertains to cyclic polypeptides I [R1 = alkyl; R2 = H, alkyl; R3 = H, alkyl; R4 = Ph, Ph substituted with 1 or more halo, OH, or alkoxy substituents; R5 = OH, NH2; A = L-Glu, L-Asp, L-Lys, L-Orn, L-2,4-diaminobutyric acid; B = L-Ala, L-Gln; C = L-Arg, D-Arg; D = L-Lys, L-Orn, L-2,4-diaminobutyric acid, L-Glu, L-Asp; E = bond, L-Lys, D-Lys; m = 0, 1; * = asym. C which may be in the D- or L-configuration; with

provisos that (a) when A = L-Glu or L-Asp, D = L-Lys, L-Orn, L-2,4-diaminobutyric acid; and (b) when A = L-Lys, L-Orn, L-2,4-diaminobutyric acid, D = L-Glu or L-Asp] including optically active isomeric forms and pharmaceutically acceptable acid addition salts thereof, having gastrointestinal motor stimulating activity. This invention also pertains to methods for using the novel cyclic polypeptides. Thus, cyclo10,14[Asp10,Leu13,Lys14]motilin(1-14) amide (porcine) (I; m = 0, R2 = R3 = H, R4 = Ph, A = Asp, B = Gln, C = Arg, D = Lys, E = bond, R5 = NH2; * = L-configuration) (II) was prepared as its bis(trifluoroacetate) salt by standard solid-phase methods on an MBHA resin using N-tert-butoxycarbonyl (Boc) amino acids. II and related cyclopeptides were tested as **motilin receptor** agonists in binding and contractility expts.

L19 ANSWER 185 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:423584 BIOSIS
DOCUMENT NUMBER: PREV199799722787
TITLE: In vitro and in vivo investigations of the effect of Leu13-porcine motilin on pig gastrointestinal motility.
AUTHOR(S): Kitazawa, T. [Reprint author]; Kikui, S. [Reprint author]; Taneike, T. [Reprint author]; Ohga, A. [Reprint author]; Sugisaka, K.; Tomizawa, N.; Hara, S.
CORPORATE SOURCE: Dep. Veterinary Pharmacol., Fac. Veterinary Med., Rakuno Gakuen Univ., Ebetsu 069, Japan
SOURCE: Laplace, J.-P. [Editor]; Fevrier, C. [Editor]; Barbeau, A. [Editor]. EUR ASS ANIM PROD PUBL, (1997) pp. 158-162. EAAP Publication; Digestive physiology in pigs.
Publisher: INRA (Institut National de la Recherche Agronomique), 147 rue de l'Universite, 75007 Paris, France.
Series: EAAP Publication.
Meeting Info.: VIIth International Symposium. Saint Malo, France. 1997.
CODEN: EAAPAN. ISSN: 0071-2477. ISBN: 2-7380-0749-X.
DOCUMENT TYPE: Book; (Book Chapter)
Conference; (Meeting Paper)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 1997
Last Updated on STN: 21 Nov 1997

L19 ANSWER 186 OF 391 MEDLINE on STN DUPLICATE 86
ACCESSION NUMBER: 1998100362 MEDLINE
DOCUMENT NUMBER: 98100362 PubMed ID: 9437708
TITLE: Identification of motilin mRNA in the brain of man and rabbit. Conservation of polymorphism of the motilin gene across species.
AUTHOR: Depoortere I; De Clercq P; Svoboda M; Bare L; Peeters T L
CORPORATE SOURCE: Gut Hormone Lab, Katholieke Universiteit Leuven, Belgium.
SOURCE: PEPTIDES, (1997) 18 (10) 1497-503.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980218
AB The data regarding the identity of motilin-like immunoreactivity in the central nervous system are controversial. The aim of the present study was to clarify whether motilin mRNA is present in the brain of rabbit and man. Total RNA, prepared from several regions of the rabbit brain, was subjected to RT-PCR aimed at amplifying a 294 bp cDNA fragment of the rabbit motilin precursor. The amplified product was subcloned and sequenced. The sequence showed 7 differences compared to the one reported for the duodenal precursor (1). However the duodenal precursor from the

rabbit used in the present study revealed identical substitutions. One of these, involving amino acid -11 of the signal peptide, was shown to be due to gene polymorphism, as has also been described at this site in man. By radioimmunoassay the highest concentration of motilin (fmol/mg protein) was detected in the hippocampus (4788 +/- 295), the lowest in the telencephalon (2127 +/- 221). Using a similar approach, but starting from commercial human brain mRNA, the sequence of a comparable cDNA fragment of the human brain motilin precursor was obtained. Its sequence was identical with the one published for the human intestinal precursor (41). Our study demonstrates that motilin mRNA is present in the brain of man and rabbit. Together with our recent findings of central **motilin receptors**, they suggest a central role for motilin.

L19 ANSWER 187 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:281481 BIOSIS
DOCUMENT NUMBER: PREV199799580684
TITLE: Inverse regulation of motilin and **motilin receptors** in inflamed and non-inflamed areas during TNBS-induced colitis in rabbits.
AUTHOR(S): Depoortere, I.; Van Assche, G.; Peeters, T. L.
CORPORATE SOURCE: Gut Hormone Lab. KU Leuven, Leuven, Belgium
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A1142. Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 3 Jul 1997

L19 ANSWER 188 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:362138 SCISEARCH
THE GENUINE ARTICLE: WV419
TITLE: Inverse regulation of motilin and **motilin receptors** in inflamed and non-inflamed areas during TNBS-induced colitis in rabbits.
AUTHOR: Depoortere I (Reprint); Vanassche G; Peeters T L
CORPORATE SOURCE: KATHOLIEKE UNIV LEUVEN, GUR HORMONE LAB, B-3001 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1997) Vol. 112, No. 4, Supp. [S], pp. A1142-A1142.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 189 OF 391 MEDLINE on STN DUPLICATE 87
ACCESSION NUMBER: 97347086 MEDLINE
DOCUMENT NUMBER: 97347086 PubMed ID: 9203450
TITLE: Erythromycin derivative improves gastric emptying and insulin requirement in diabetic patients with gastroparesis.
AUTHOR: Ishii M; Nakamura T; Kasai F; Baba T; Takebe K
CORPORATE SOURCE: Medical Check-up Centre, Hakodate Chuo Hospital, Japan.
SOURCE: DIABETES CARE, (1997 Jul) 20 (7) 1134-7.
Journal code: 7805975. ISSN: 0149-5992.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971219

AB OBJECTIVE: To evaluate the effect of the erythromycin derivative EM523L on gastric emptying and postprandial insulin requirement in insulin-dependent diabetic patients with severe gastroparesis. RESEARCH DESIGN AND METHODS: In six IDDM patients with severe gastroparesis (two men and four women, mean age 44.5 years [range 36-53]), the insulin infusion pattern during feedback control with an artificial endocrine pancreas device (Biostator) after intake of a test meal, the retention rate of residual isotope ([99m]Tc-labelled Sn-colloid) in the stomach, and the time-concentration curve of plasma acetaminophen as the marker for liquid emptying were studied with EM523L or a control placebo RESULTS: Time courses of insulin infusion rates peaked within 120 min after intake of the test meal in the EM523L phase, whereas no apparent peak rates were observed in the control phase. The total amount of insulin required in the first 90 min postprandial was significantly greater in the EM523L phase than in the control phase. EM523L significantly decreased the residual isotope ratio in the stomach at > or =50 min postprandial and increased the plasma acetaminophen concentrations at 30-120 min postprandial, compared with respective values in the control phase. CONCLUSIONS: Preliminary results obtained from a small number of patients suggest that EM523L or erythromycin analogs, which have agonistic activity to **motilin receptors** as well as no antibacterial effect, may be useful to accelerate gastric emptying and improve insulin requirement patterns, thereby establishing more stable glycemic control.

L19 ANSWER 190 OF 391 MEDLINE on STN DUPLICATE 88
ACCESSION NUMBER: 97319303 MEDLINE
DOCUMENT NUMBER: 97319303 PubMed ID: 9176206
TITLE: Demonstration and characterization of motilin-binding sites in the rabbit cerebellum.
AUTHOR: Depoortere I; Peeters T L
CORPORATE SOURCE: Department of Pathophysiology, Katholieke Universiteit Leuven, Belgium.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1997 May) 272 (5 Pt 1) G994-9.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 20000303
Entered Medline: 19970708

AB This is the first report on central **motilin receptors.** Autoradiography on cerebellar slices revealed specific motilin-binding sites in the molecular layer of the cortex. Scatchard analysis of cold saturation studies showed the existence of a high-(pKd,hi = 9.07 +/- 0.09, where pKd is the negative logarithm of the dissociation constant) and a low-affinity binding site (pKd,lo = 6.56 +/- 0.09). Similar affinities were found with rabbit motilin and with the porcine (po) antagonist [Phe3, Leu13]po-motilin. Feline and canine motilin had a markedly lower affinity for the low-affinity site (pKd,lo = 5.29 and 4.58, respectively); chicken motilin had a lower affinity for both sites (pKd,hi = 8.36, pKd,lo = 3.97). Erythromycin A and its derivative N-trimethyl erythromycin A cnol ether also bound to cerebellar **motilin receptors** (pKd,hi = 7.29 and 8.91, respectively). Structure-activity studies with motilin fragments and the potency ranking of agonists suggest that a novel subtype receptor of motilin may exist in the brain. Guanosine

5'-O-(3-thiotriphosphate) (0.1 mM) reduced the number and the affinity for the high-affinity binding sites, which is evidence for G protein-coupled receptors. Our findings open new perspectives for the study of the physiological role of motilin.

L19 ANSWER 191 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:399587 SCISEARCH
THE GENUINE ARTICLE: WZ327
TITLE: Demonstration and characterization of motilin-binding sites in the rabbit cerebellum
AUTHOR: Depoortere I; Peeters T L (Reprint)
CORPORATE SOURCE: GASTHUISBERG ON, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM (Reprint); KATHOLIEKE UNIV LEUVEN, GUT HORMONE LAB, DEPT PATHOPHYSIOL, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (MAY 1997) Vol. 35, No. 5, pp. G994-G999. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0193-1857.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This is the first report on central **motilin receptors**. Autoradiography on cerebellar slices revealed specific motilin-binding sites in the molecular layer of the cortex. Scatchard analysis of cold saturation studies showed the existence of a high- (PKd,hi = 9.07 +/- 0.09, where pK(d) is the negative logarithm of the dissociation constant) and a low-affnity binding site (pK(d,lo) = 6.56 +/- 0.09). Similar affinities were found with rabbit motilin and with the porcine (po) antagonist [Phe(3),Leu(13)]po-motilin. Feline and canine motilin had a markedly lower affinity for the low-affinity site (pK(d,lo) = 5.29 and 4.58, respectively); chicken motilin had a lower affinity for both sites (PKd,hi = 8.36, PKd,lo = 3.97). Erythromycin A and its derivative N-trimethyl erythromycin A enol ether also bound to cerebellar **motilin receptors** (pK(d,hi) = 7.29 and 8.91, respectively). Structure-activity studies with motilin fragments and the potency ranking of agonists suggest that a novel subtype receptor of motilin may exist in the brain. Guanosine 5'-O-(3-thiotriphosphate) (0.1 mM) reduced the number and the affinity for the high-affinity binding sites, which is evidence for G protein-coupled receptors. Our findings open new perspectives for the study of the physiological role of motilin.

L19 ANSWER 192 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:280260 BIOSIS
DOCUMENT NUMBER: PREV199799579463
TITLE: Effects of EM574 and cisapride on solid and liquid gastric emptying and motility in normal and gastroparesis dogs.
AUTHOR(S): Tanaka, T.; Mizumoto, A.; Itoh, Z.
CORPORATE SOURCE: GI Labs., Inst. Molecular Cellular Regulation, Gunma Univ. Sch. Med., Maebashi, Japan
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A836. Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 3 Jul 1997

L19 ANSWER 193 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1997:280073 BIOSIS
DOCUMENT NUMBER: PREV199799579276
TITLE: Characterization of neural **motilin receptors** in human antrum.
AUTHOR(S): Miller, P.; Roy, A.; Dagenais, M.; Lapointe, R.; Trudel, L.; Poitras, P.
CORPORATE SOURCE: Hop. St. Luc, Univ. Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A789. Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 3 Jul 1997

L19 ANSWER 194 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:360732 SCISEARCH
THE GENUINE ARTICLE: WV419
TITLE: Characterization of neural **motilin receptors** in human antrum
AUTHOR: Miller P (Reprint); Roy A; Dagenais M; Lapointe R; Trudel L; Poitras P
CORPORATE SOURCE: UNIV MONTREAL, HOP ST LUC, MONTREAL, PQ, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1997) Vol. 112, No. 4, Supp. [S], pp. A789-A789.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 195 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:279801 BIOSIS
DOCUMENT NUMBER: PREV199799579004
TITLE: Inhibitory effects of motilides at high concentrations are not mediated via **motilin receptors**, but via calcium channels.
AUTHOR(S): Depoortere, I.; Peeters, T. L.
CORPORATE SOURCE: Gut Hormone Lab., Gasthuisberg ON, B-3000 Leuven, Belgium
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A721. Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 3 Jul 1997

L19 ANSWER 196 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:360461 SCISEARCH
THE GENUINE ARTICLE: WV419
TITLE: Inhibitory effects of motilides at high concentrations are not mediated via **motilin receptors**, but via calcium channels
AUTHOR: Depoortere I (Reprint); Peeters T L
CORPORATE SOURCE: UNIV HOSP GASTHUISBERG, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM

COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1997) Vol. 112, No. 4, Supp. [S], pp. A721-A721.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L19 ANSWER 197 OF 391 MEDLINE on STN DUPLICATE 89
ACCESSION NUMBER: 97289201 MEDLINE
DOCUMENT NUMBER: 97289201 PubMed ID: 9144124
TITLE: Antroduodenal motor effects of intravenous erythromycin in children with abnormalities of gastrointestinal motility.
AUTHOR: Cucchiara S; Minella R; Scoppa A; Emiliano M; Calabrese F; Az-Zeqeh N; Rea E; Salvia G
CORPORATE SOURCE: Department of Pediatrics, School of Medicine, University of Naples Federico II, Italy.
SOURCE: JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, (1997 Apr) 24 (4) 411-8.
Journal code: 8211545. ISSN: 0277-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 19970724
Entered Medline: 19970714

AB BACKGROUND: The macrolide antibiotic erythromycin (EM) affects gastrointestinal motor activity by acting as agonist of **motilin receptors** located on the smooth muscle cells of the gastroduodenal tract. We studied the effect of intravenous EM on fasting antroduodenal motility in controls and children with gastrointestinal dysmotility. METHODS: EM lactobionate (rate, 3.0 mg/kg/h) was infused intravenously while antroduodenal manometry was recorded in 10 controls, in 7 patients with functional dyspepsia and in 6 patients with gut pseudo-obstruction. The mean (SD) age (years) was 5.7 (1.4), 6.5 (2.4), and 6.7 (3.2), respectively. Manometry was performed by means of a four- or six-lumen catheter introduced through the nose and perfused with a low compliance pneumohydraulic system. Five controls received EM and five received saline. RESULTS: EM, infused 5 minutes after passage of an activity front (AF), induced in controls a premature antroduodenal AF occurring 15.4 +/- 3.2 minutes after starting infusion; no motor changes were seen after saline; duration and propagation velocity of EM-induced AFs did not differ from spontaneous AFs. In patients with functional dyspepsia EM induced various patterns such as premature antroduodenal AFs, antral phase III-like pattern with short duodenal bursts or prolonged phasic antral waves and no duodenal activity. In patients with neurogenic pseudo-obstruction rare or absent antral activity with incoordinated or absent duodenal activity was induced; no contractions were elicited in two patients with myogenic pseudo-obstruction. CONCLUSIONS: It is confirmed that EM, given at subtherapeutic doses, is a powerful prokinetic agent that can have clinical applications in patients with gastrointestinal dysmotility; however, the effect of the drug seems to be influenced by the nature of the underlying disorder.

L19 ANSWER 198 OF 391 MEDLINE on STN DUPLICATE 90
ACCESSION NUMBER: 97428090 MEDLINE
DOCUMENT NUMBER: 97428090 PubMed ID: 9284278
TITLE: Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants.
AUTHOR: Jadcherla S R; Klee G; Berseth C L

CORPORATE SOURCE: Department of Pediatrics, Baylor College of Medicine Affiliated Hospitals, Houston, Texas 77030, USA.
SOURCE: PEDIATRIC RESEARCH, (1997 Sep) 42 (3) 365-9.
Journal code: 0100714. ISSN: 0031-3998.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971124

AB In adults, migrating motor complexes (MMCs) appear to be partially under hormonal modulation by motilin and pancreatic polypeptide. Preterm infants do not exhibit MMCs until 32 wk of gestation. Although plasma concentrations of motilin are similar in infants and adults, it is not known if actual hormonal modulation of MMCs is present in infants. In the first study we assessed whether plasma concentrations of motilin and pancreatic polypeptide surge with the occurrence of MMCs in term infants. In the second study we assessed whether erythromycin, a **motilin receptor** agonist, could induce migrating motor activity in preterm and term infants. In the first study we recorded motor activity in nine term infants who had never been fed. We determined plasma concentrations of motilin and pancreatic polypeptide in the presence and absence of MMCs. In the second study we gave the motilin agonist erythromycin intragastrically to 21 infants at a range of 24-42 wk of gestation to assess whether migrating activity could be induced via the **motilin receptor.** In the first study, plasma concentrations of motilin were similar during the presence and absence of MMCs, as were plasma concentrations of pancreatic polypeptide. In the second study, the administration of erythromycin induced the appearance of migrating activity in 7 of 14 infants who were older than 32 wk but in none of the infants who was younger than 32 wk. Although the **motilin receptor** appears to be functionally present beyond 32 wk of gestation, as assessed by in indirect pharmacologic challenge, hormonal modulation of migrating activity in the neonate by plasma motilin and pancreatic polypeptide is absent.

L19 ANSWER 199 OF 391 MEDLINE on STN
ACCESSION NUMBER: 97351718 MEDLINE
DOCUMENT NUMBER: 97351718 PubMed ID: 9208000
TITLE: [Acute reversible pan-dysautonomia: effect of erythromycin on gastrointestinal involvement].
Pan-dysautonomie aigue reversible: effet de l'erythromycine sur l'atteinte gastro-intestinale.
COMMENT: Comment in: Gastroenterol Clin Biol. 1997;21(12):994-6
AUTHOR: Lagasse J P; Picon L; Metman E H; Babuty D; Degiovanni E; Huten N
CORPORATE SOURCE: Service de Gastroenterologie, CHRU, Tours.
SOURCE: GASTROENTEROLOGIE CLINIQUE ET BIOLOGIQUE, (1997) 21 (4) 331-4. Ref: 12
Journal code: 7704825. ISSN: 0399-8320.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19990129
Entered Medline: 19970806

AB We describe a case of acute autonomic neuropathy in an 18-year-old woman. Gut dysfunction was sufficiently severe for the patient to undergo laparotomy for suspected mechanical-intestinal obstruction before the

diagnosis was made. Apart from the gut, other organs affected included the pupils, sweat and lachrymal glands. Cardiovascular autonomic function tests showed the involvement of sympathetic adrenergic nerves. Small bowel barium X-ray showed resolution of gastric stasis and emergence of jejunum dilatation during intravenous administration of erythromycin but this treatment did not eliminate intestinal obstructive symptoms. The patient had an incomplete recovery in 3 months. Erythromycin might have therapeutic value in patients with intestinal motility dysfunction in acute dysautonomia.

L19 ANSWER 200 OF 391 MEDLINE on STN DUPLICATE 91
ACCESSION NUMBER: 1998090289 MEDLINE
DOCUMENT NUMBER: 98090289 PubMed ID: 9430424
TITLE: Concentration-dependent stimulation of cholinergic motor nerves or smooth muscle by [Nle13]motilin in the isolated rabbit gastric antrum.
AUTHOR: Van Assche G; Depoortere I; Thijs T; Janssens J J; Peeters T L
CORPORATE SOURCE: Department of Pathophysiology, University of Leuven, Belgium.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1997 Oct 22) 337 (2-3) 267-74.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 19980312
Entered Medline: 19980303

AB In man, rabbit and cat, the effects of motilin and motilides are neurally mediated in vivo, whereas in vitro binding and contractility studies suggest the presence of a smooth muscular receptor. The aim of this study was to investigate in vitro interactions of motilin with the enteric excitatory neurotransmission in the gastric antrum of the rabbit. Circular muscle strips from the pre-pyloric antrum were subjected to electrical field stimulation (1 ms, 1-32 Hz, 10 s train) and muscle twitch responses were recorded isometrically. Induced twitch responses were frequency dependent (1-32 Hz) and entirely neurogenic (tetrodotoxin sensitive). [Nle13]motilin dose-dependently (10[-9]-10[-8] M) enhanced the amplitude of, atropine sensitive, evoked contractions. At 4 Hz the response, expressed as a % of the response to 32 Hz, increased from 15.5 +/- 4.1% (control) to 28.1 +/- 5.8% (motilin 10[-9] M), and to 45.8 +/- 3.6% (motilin 10[-8.5] M) ($P < 0.05$). This effect was not inhibited by hexamethonium (10[-3.3] M) but was abolished by the **motilin receptor** antagonist GM-109 (10[-5] M). In unstimulated strips, motilin induced phasic-tonic contractions with a threshold concentration of 10[-8] M and an pEC50 of 7.48, which were also inhibited by GM-109 (10[-5] M) but not by tetrodotoxin (10[-5.5] M). The maximal tension, frequency and dose-dependency of carbachol-induced contractions were not influenced by motilin (pEC50, carbachol: 6.48 +/- 0.06 (control), 6.49 +/- 0.07 (motilin)). In conclusion, motilin enhances contractions induced by electrical field stimulation in the rabbit antrum by a post-ganglionic interaction with the cholinergic neurotransmission in vitro at low doses and interacts directly with antral smooth muscle at high doses. This model is an accurate reflection of the in vivo effects of motilin and provides a tool to study neurogenic and myogenic actions of motilin and motilides in vitro.

L19 ANSWER 201 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:438997 CAPLUS
DOCUMENT NUMBER: 127:117648
TITLE: In vitro and in vivo investigations of the effect of Leu13-porcine motilin on pig gastrointestinal motility

AUTHOR(S): Kitazawa, T.; Kikui, S.; Taneike, T.; Ohga, A.; Sugisaki, K.; Tomizawa, N.; Hara, S.
CORPORATE SOURCE: Department of Veterinary Pharmacology, Faculty of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, 069, Japan
SOURCE: EAAP Publication (1997), 88(Digestive Physiology in Pigs), 158-162
CODEN: EAAPAN; ISSN: 0259-322X
PUBLISHER: Institut National de la Recherche Agronomique
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The physiol. role of motilin in the pig gastrointestinal (GI) motility was investigated in vitro and in vivo studies. In the in vitro study, Leu13-porcine motilin (LMT, 1 nM-10 μM) produced no mech. response in either longitudinal or circular muscle strips of the stomach and duodenum. Dispersed cells of the duodenum also did not respond to LMT. In elec. stimulated gastric and duodenal strips, LMT did not modify the cholinergic contraction and the non-adrenergic, non-cholinergic relaxation. In the in vivo study, LMT given i.v. at 0.3 μg/kg or more caused contractions of the stomach (corpus, antrum) but not of the small intestine (duodenum, jejunum) in the fasting state. The responses of LMT were inhibited by atropine and hexamethonium but not by phentolamine and propranolol. The present results indicate that motilin stimulates gastric motility in the pig, but that functional **motilin receptors** do not exist on smooth muscle cells and efferent neurons in the GI tract.

L19 ANSWER 202 OF 391 MEDLINE on STN DUPLICATE 92
ACCESSION NUMBER: 97321229 MEDLINE
DOCUMENT NUMBER: 97321229 PubMed ID: 9177950
TITLE: Pharmacological stimulation of gastrointestinal motility: where we are and where are we going?.
AUTHOR: Scarpignato C
CORPORATE SOURCE: Institute of Pharmacology, School of Medicine and Dentistry, University of Parma, Italy.
SOURCE: DIGESTIVE DISEASES, (1997) 15 Suppl 1 112-36. Ref: 134
Journal code: 8701186. ISSN: 0257-2753.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 19970805
Entered Medline: 19970723

AB Drugs affecting gastrointestinal motility have become valuable in the management of a number of diseases. Medications that enhance the transit of material through the gastrointestinal tract are called prokinetics. Although symptom improvement can be seen in a variety of motility disorders, these medications have not shown a selective benefit for a particular motility disturbance or symptom complex. This class of drugs includes several subclasses, each with a distinct mechanism of action. Amongst the existing prokinetic compounds, dopamine antagonists, on the one hand, and cholinomimetic drugs, on the other hand, should be distinguished. Since compounds endowed with dopamine antagonism have the disadvantage of causing neuroendocrine side effects and/or extrapyramidal dyskinetic reactions (seen especially after metoclopramide), the recently developed non-cholinergic non-antidopaminergic compound, cisapride, seems to be the most effective one. Its main mechanism of action is considered to be the stimulation of myenteric cholinergic nerves with consequent increase of acetylcholine release. Recent evidence suggests that blockade of CCK receptors and stimulation of **motilin receptors** are also promising avenues to increase gastrointestinal motility. Since drugs acting on 5-HT receptors are presently the best available

motor-stimulating compounds, new derivatives are being developed as gastrokinetic drugs. Although the long-acting somatostatin analog, octreotide, and the GnRH agonist, leuprolide, have shown prokinetic properties in particular clinical conditions, their widespread use cannot be recommended at present. Further work is needed to determine the predictive value of objective abnormalities for the efficacy of a drug in the individual patient. This is the crucial point to define a rational strategy in clinical practice, especially to establish if functional investigation is needed before a prokinetic drug be given.

L19 ANSWER 203 OF 391 MEDLINE on STN DUPLICATE 93
ACCESSION NUMBER: 1998109472 MEDLINE
DOCUMENT NUMBER: 98109472 PubMed ID: 9449418
TITLE: Distribution and subcellular localization of motilin binding sites in the rabbit brain.
AUTHOR: Depoortere I; Van Assche G; Peeters T L
CORPORATE SOURCE: Department of Pathophysiology, University of Leuven, Gasthuisberg O and N, Belgium.
SOURCE: BRAIN RESEARCH, (1997 Nov 28) 777 (1-2) 103-9.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980224

AB We previously reported the existence of **motilin receptors** in the cerebellum of the rabbit. We now explored the existence of **motilin receptors** in other brain regions and determined their association with neurons by subcellular fractionation studies. Autoradiographic studies with [(125)I]nle13-porcine motilin on rabbit coronal brain sections revealed specific binding sites in the hippocampus, thalamus, hypothalamus and amygdaloid body. Receptor binding studies allowed the identification of two binding sites. In all regions the density of the high-affinity binding site was lower than in the cerebellum, but its affinity was the same, except for the hypothalamus. No differences were found for affinity or density of the low-affinity receptor site. Homogenates of rabbit cerebellum were subjected to differential centrifugation. The highest motilin binding (10-times more than in the postnuclear supernatant) was found in the fraction which also showed maximal enrichment of [11-3H]saxitoxin binding (selective marker for voltage-sensitive Na+ channels), 6.9-fold, and cytochrome c oxidase activity (mitochondrial marker), 2.4-fold. In discontinuous sucrose density gradient centrifugation the motilin and saxitoxin binding both peaked in the 0.85-1 M layer, while cytochrome c oxidase was maximal in the 1.2 M layer. In conclusion, **motilin receptors** exist in several regions of the rabbit brain and are probably associated with synaptosomes. These findings further support a neurotransmitter role for motilin in the brain.

L19 ANSWER 204 OF 391 MEDLINE on STN DUPLICATE 94
ACCESSION NUMBER: 1998077472 MEDLINE
DOCUMENT NUMBER: 98077472 PubMed ID: 9416990
TITLE: Functional characterization of neural and smooth muscle **motilin receptors** in the chicken proventriculus and ileum.
AUTHOR: Kitazawa T; Taneike T; Ohga A
CORPORATE SOURCE: Department of Pharmacology, Faculty of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan.
SOURCE: REGULATORY PEPTIDES, (1997 Aug 15) 71 (2) 87-95.
Journal code: 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980128

AB To characterize the **motilin receptors** present in the chicken, the effects of chicken motilin (Phe-Val-Pro-Phe-Phe-Thr-Gln-Ser-Asp-Ile-Gln-Lys-Met-Gln-Glu-Lys-Glu-Arg -Asn-Lys-Gly-Gln), Leu13 porcine motilin, canine motilin and three erythromycin derivatives (EMA, EM523, GM611) on the contractility of the chicken gastrointestinal (GI) smooth muscles were investigated in vitro and compared with those in the rabbit duodenum. In the proventriculus longitudinal and circular muscle layers, chicken motilin (3 nM-1 microM) caused an atropine- and a tetrodotoxin-sensitive contraction (EC50 = 39-49 nM), and potentiated the EFS-induced contraction without affecting the responsiveness of acetylcholine. EM523 and GM611 (3-100 microM) contracted the proventriculus longitudinal muscle, and the maximum amplitudes of contraction were about 60% of that induced by chicken motilin. Chicken motilin (0.1 nM-100 nM) also caused contraction of the ileum (EC50 = 7 nM) through direct action on the smooth muscle cells. On the other hand, erythromycin derivatives showed only a weak contractile efficacy (about 20% of the maximum response of chicken motilin) even at high concentrations (10-100 microM). The rank order of potency in the ileum was chicken motilin > canine motilin > or = Leu13 porcine motilin > > GM611 > or = EM523 > or = EMA. GM109 slightly inhibited the ideal contractions induced by Leu13 porcine motilin at 100 microM (pA2 = 3.86). In the rabbit duodenum, chicken motilin was a full agonist with the same intrinsic activity as Leu13 porcine motilin, canine motilin and the erythromycin derivatives. However, the rank order of potency (Leu13 porcine motilin > or = canine motilin > chicken motilin > GM611 > or = EM523 > EMA) was different from that in the chicken ileum. In conclusion, chicken motilin causes an excitatory response in the chicken GI tract through activation of neural (proventriculus) and smooth muscle **motilin receptors** (ileum). The **motilin receptor** present in the ileum is different from that demonstrated in the rabbit intestine, because of a different rank order of motilin peptides in producing the contraction, low contracting activity of erythromycin derivatives and low antagonistic efficacy of GM109. Different pharmacological characteristics of the mechanical response induced by motilin peptides and erythromycin derivatives between the proventriculus and the ileum are discussed.

L19 ANSWER 205 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:679445 CAPLUS
DOCUMENT NUMBER: 132:178285
TITLE: Characterization of **motilin receptor** in the chicken gastrointestinal tract
AUTHOR(S): Kitazawa, Takio; Kanaya, Shizuka; Taneike, Tetsuro
CORPORATE SOURCE: Department of Pharmacology, Faculty of Veterinary Medicine, Rakuno Gakuen University, Japan
SOURCE: Shokakan Horumon (XV), Gut Hormone Kanfaransu Kirokushu -- 18th, Japan, 1996 (1997), Meeting Date 1996, 86-90. Igaku Tosho Shuppan K.K.: Tokyo, Japan. CODEN: 68HLAU
DOCUMENT TYPE: Conference
LANGUAGE: Japanese

AB Marked contraction of chicken gastrointestinal smooth muscle was observed in the presence of chicken motilin via **motilin receptors.** The **motilin receptors** of chicken showed different contraction induction and other muscular activities as compared to those of rabbit **motilin receptors**, indicating structural differences between the **motilin receptors** of chicken and rabbits.

L19 ANSWER 206 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:792164 CAPLUS
DOCUMENT NUMBER: 128:83973
TITLE: Motilin and the discovery and development of motilinomimetics
AUTHOR(S): Peeters, Theo L.
CORPORATE SOURCE: Centre for Gastroenterological Research, University of Leuven, Louvain, B-3000, Belg.
SOURCE: Old Herborn University Seminar Monograph (1997), 9(Gastro-Intestinal Motility), 77-87
CODEN: OHUME5; ISSN: 1431-6579
PUBLISHER: Institute for Microbiology and Biochemistry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with over 40 refs. Motilin is a peptide which stimulates gastro-intestinal motor activity. Motilin has been mostly studied in relation to the migrating motor complex, and is thought to be involved in the regulation of this pattern. Motilin also increases pressure in the lower esophageal sphincter, accelerates gastric emptying, induces gallbladder contraction and increases colon motility. Smooth muscle **motilin receptors** have been characterized pharmacol. in several species and organ-specific subtypes may exist. The existence of neuronal **motilin receptors** can be deduced from in vivo data. They probably resemble the smooth muscle receptors, and may be even closer related to the recently discovered central **motilin receptors.** Erythromycin has been shown to be a motilin agonist. The development of motilin antagonists has removed all doubt in this regard. The successful application of erythromycin in patients with gastroparesis has stimulated the development of motilinomimetics, a new class of prokinetic drugs. This class encompasses motilides, derived from macrolides, and motilin analogs. Several motilides have already been proposed as well as two motilin analogs, and affinity for the **motilin receptor** has been a useful screening tool in their development. At the same time these studies have led to an understanding of the structure-activity relation of motilin, and to the development of antagonists. The **motilin receptor** may also be used to develop antibiotics with reduced gastro-intestinal side-effects. One may safely predict that soon motilinomimetics will be available for the treatment of hypomotility conditions. This will again increase our understanding of the physiol. role of motilin and of the regulation of gastro-intestinal motility.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 207 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:138206 SCISEARCH
THE GENUINE ARTICLE: WG271
TITLE: Neural mediation of the motilin motor effect on the human antrum
AUTHOR: Boivin M; Pinelo L R; StPierre S S; Poitras P (Reprint)
CORPORATE SOURCE: UNIV MONTREAL, HOP ST LUC, CTR RECH CLIN ANDRE VIALLET, 264 BOUL RENE LEVESQUE E, MONTREAL, PQ H2X 1P1, CANADA (Reprint); UNIV MONTREAL, HOP ST LUC, CTR RECH CLIN ANDRE VIALLET, MONTREAL, PQ H2X 1P1, CANADA; UNIV QUEBEC, INST NATL RECH SCI SANTE, MONTREAL, PQ H2X 1P1, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (JAN 1997) Vol. 35, No. 1, pp. G71-G76.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0193-1857.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To elucidate the mode of action of motilin on the stimulation of human gastrointestinal motility, we studied the effect of exogenous motilin during muscarinic or serotoninergic pharmacological blockade. Manometric recording of the interdigestive antroduodenal motility was carried out in 27 healthy volunteers until the appearance of a spontaneous antral phase III. The tested blocker was then administered intravenously and was followed 30 min later by a 10-min infusion of synthetic human motilin (50 ng/kg). Motilin administered on a background of saline induced a premature phase III migrating from the antrum to the duodenum in every tested subject (n = 5). A low dose of atropine (5 mu g . kg(-1). h(-1) for 90 min) inhibited the motilin effect in two of five subjects [not significant (NS)], whereas a high dose of atropine (15 mu g/kg given in 30 min) blocked the motilin-induced premature antral phase III in all instances (n = 5, P < 0.01). Exogenous motilin given with low-dose ondansetron (8 mg given in 15 min followed by 1 mg/h for 90 min) or high-dose ondansetron (32 mg given in 30 min) was without effect in three of seven (NS) or in two of five (NS) subjects, respectively. During the administration of 15 mu g/kg atropine, when exogenous motilin always failed to induce a premature antral phase III motor, a phase III-type activity was generated at the duodenum in four of five subjects. We conclude that the induction by motilin of phase III activity in human antrum is dependent on muscarinic mediation and that the contractile effect of motilin on human duodenum involves a noncholinergic mechanism, different therefore from the antral pathway.

L19 ANSWER 208 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:256732 SCISEARCH
THE GENUINE ARTICLE: WP796
TITLE: In vivo characterization of the colonic prokinetic effect of erythromycin in the rabbit
AUTHOR: Costa A; DePonti F (Reprint); Crema F; dAngelo L
CORPORATE SOURCE: UNIV PAVIA, DEPT INTERNAL MED & THERAPEUT, SECT PHARMACOL & TOXICOL, I-27100 PAVIA, PV, ITALY (Reprint); UNIV PAVIA, DEPT INTERNAL MED & THERAPEUT, SECT PHARMACOL & TOXICOL, I-27100 PAVIA, PV, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: PHARMACOLOGY, (FEB 1997) Vol. 54, No. 2, pp. 64-75. Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 0031-7012.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The motor effect of erythromycin was characterized in conscious rabbits chronically fitted with electrodes and strain-gauge force transducers implanted along the proximal and distal colon. Fecal pellet output was also evaluated as an index of propulsive activity. In order to get an insight into the pathways involved in mediating the effect of erythromycin, the macrolide was also administered after pretreatment with atropine, nifedipine or ondansetron. Furthermore, in vitro experiments with erythromycin alone and in the presence of atropine, nifedipine, tetrodotoxin or ondansetron were carried out with circular muscle strips taken from rabbit distal colon. In vivo, erythromycin (0.087-5.6 mg/kg i.v. bolus) dose-dependently stimulated spike and mechanical activities at both colonic levels, with a more marked effect on the distal colon. Erythromycin also dose-dependently increased the number of aborally migrating long spike bursts and fecal pellet output. The reproducibility of the response to erythromycin was confirmed by experiments with the dose of 2.8 mg/kg i.v. bolus, repeated in five consecutive experiments at 48-hour intervals. Nifedipine, but not atropine or ondansetron, significantly reduced the colonic motor response to erythromycin. In vitro experiments gave results in line with the in vivo data: the

concentration-dependent contractile effect of erythromycin was almost suppressed by nifedipine, but resistant to atropine, tetrodotoxin or ondansetron. In conclusion, this study provides evidence that: (1) erythromycin is a prokinetic drug at the colonic level in rabbits, and (2) both in vivo and in vitro, the effects of erythromycin are exerted at the smooth muscle level by mechanisms depending on influx of extracellular calcium, while muscarinic and 5-HT3 receptors are not involved, at least in this model.

L19 ANSWER 209 OF 391 MEDLINE on STN DUPLICATE 95
ACCESSION NUMBER: 97244061 MEDLINE
DOCUMENT NUMBER: 97244061 PubMed ID: 9088872
TITLE: EM574, an erythromycin derivative, is a **motilin receptor** agonist in the rabbit.
AUTHOR: Sato F; Sekiguchi M; Marui S; Inatomi N; Shino A; Itoh Z; Omura S
CORPORATE SOURCE: Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Ltd., Osaka, Japan.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1997 Mar 12) 322 (1) 63-71.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970721
Last Updated on STN: 19970721
Entered Medline: 19970707
AB This study was performed to examine whether an erythromycin derivative, de(N-methyl)-N-isopropyl-8,9-anhydroerythromycin A 6,9-hemiacetal (EM574) is a **motilin receptor** agonist in the rabbit gastrointestinal tract. EM574 and porcine motilin induced contractions in segments of isolated rabbit intestine with pEC50 values of 8.26 +/- 0.04 and 8.69 +/- 0.07, respectively, but not in rat or guinea pig preparations. The sensitivity and efficacy of the response to both compounds in rabbits decreased aborally and was insensitive to pretreatment with atropine or tetrodotoxin, but was markedly suppressed under Ca(2+)-free conditions. EM574 and porcine motilin specifically displaced [125I-Tyr23]canine motilin bound to gastric antral smooth muscle homogenates with plC50 values of 8.21 +/- 0.13 and 9.20 +/- 0.11, respectively. The pEC50 value for the contractile response and plC50 value for the receptor binding for motilin, EM574, erythromycin A and three other derivatives correlated well ($r = 0.94$, $P < 0.01$). Tissue section autoradiography in the antrum revealed that specific labeled motilin binding sites were localized in the circular muscle layer and myenteric plexus, and could be reduced in the presence of an excess of EM574. These results indicate that EM574 is a potent **motilin receptor** agonist in the rabbit gastrointestinal tract.

L19 ANSWER 210 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 96:898213 SCISEARCH
THE GENUINE ARTICLE: VV476
TITLE: Effect of bethanechol or erythromycin on gastric emptying in houses
AUTHOR: Ringger N C (Reprint); Lester G D; Neuwirth L; Merritt A M; Vetro T; Harrison J
CORPORATE SOURCE: UNIV FLORIDA, ISL WHIRL EQUINE COL RES LAB, DEPT LARGE ANIM CLIN SCI, GAINESVILLE, FL 32610 (Reprint); UNIV FLORIDA, INST FOOD & AGR SCI, DEPT STAT, GAINESVILLE, FL 32610
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF VETERINARY RESEARCH, (DEC 1996) Vol. 57, No. 12, pp. 1771-1775.
Publisher: AMER VETERINARY MEDICAL ASSOC, 1931 N MEACHAM

RD SUITE 100, SCHAUMBURG, IL 60173-4360.
ISSN: 0002-9645.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: AGRI
LANGUAGE: English
REFERENCE COUNT: 75
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective-To investigate the prokinetic effect of bethanechol and erythromycin in the upper gastrointestinal tract of healthy horses by measuring the gastric emptying (GE) rate of a radioactive meal.

Animals-4 healthy adult horses.

Procedure-After food was withheld for 12 hours, horses were given 370 MBq of Tc-99m-labeled sulfur colloid incorporated into egg albumen and 37 MBq of (111)In-labeled diethyltriaminepentaacetic acid in 120 ml of water via nasogastric intubation. Intravenously administered treatments were 0.9% NaCl solution, erythromycin (0.1 or 1.0 mg/kg of body weight), or bethanechol (0.25 mg/kg). All drugs were given in 10 ml of 0.9% NaCl solution. Dual-phase scintigraphic images were obtained by use of a gamma camera. The best-fit function was determined for each study, and the resultant curves were then analyzed by use of least squares nonlinear regression. Two variables, time to 50% emptying of the stomach (T-50) and slope of the emptying curve, were derived from the calculated power exponential equation.

Conclusions-Treatment had a significant ($P < 0.05$) overall effect on T-50 of solid-phase GE. The T-50 of bethanechol (30.09 +/- 10.01 minutes), erythromycin at 0.1 mg/kg (59.08 +/- 10.01 minutes), and erythromycin at 1 mg/kg (60.50 +/- 10.01 minutes) were significantly shorter than T-50 after saline administration (89.97 +/- 10.01 minutes). There was a trend ($P = 0.09$) for the slope of solid-phase GE of bethanechol and erythromycin (0.1 mg/kg; $P = 0.37$) to be steeper than that of saline solution. For liquid-phase GE, the T-50 and the slope of bethanechol differed significantly (P less than or equal to 0.05) from those for saline solution.

Clinical Relevance-Bethanechol and erythromycin significantly increased solid-phase GE in healthy horses and may have value for use as prokinetic agents in certain gastrointestinal tract diseases.

L19 ANSWER 211 OF 391 MEDLINE on STN DUPLICATE 96
ACCESSION NUMBER: 97118920 MEDLINE
DOCUMENT NUMBER: 97118920 PubMed ID: 8959762
TITLE: Study of the binding of motilin to the membranes of enterocytes from rabbit jejunum.
AUTHOR: Alcalde A I; Plaza M A; Marco R
CORPORATE SOURCE: Departamento de Fisiologia, Facultad de Veterinaria, Universidad de Zaragoza, Spain.
SOURCE: PEPTIDES, (1996) 17 (7) 1237-41.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 19970327
Entered Medline: 19970314

AB The results obtained in the present work have shown that [125I]motilin bound specifically to basolateral (BL) membrane but it did not bind to the brush border (BB) membrane of the rabbit jejunum enterocyte. The [125I]motilin dissociation constant (Kd) was 95.58 +/- 15.0 pM and the receptor density (Bmax) was 2.54 +/- 0.40 fmol/mg protein. The binding of [125I]motilin to BL membrane was competitively inhibited by both unlabeled motilin and erythromycin. The IC50s were (2.1 +/- 0.4) 10(-8) M and (1.3 +/- 0.1) 10(-6) M for motilin and erythromycin, respectively, and the Ki were (6.83 +/- 1.3) 10(-9) M for motilin and (4.32 +/- 0.33) 10(-7) M for erythromycin. Saturation and competition binding studies showed

interaction at only one class of binding sites in BL membrane.

L19 ANSWER 212 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:301315 BIOSIS
DOCUMENT NUMBER: PREV199699023671
TITLE: **Motilin receptors** are located on neural membranes in the canine duodenum.
AUTHOR(S): Miller, P.; Poitras, P.
CORPORATE SOURCE: Hopital Saint-Luc, Univ. Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A1100. Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 2 Jul 1996

L19 ANSWER 213 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 96:336398 SCISEARCH
THE GENUINE ARTICLE: UF737
TITLE: **MOTILIN RECEPTORS** ARE LOCATED ON NEURAL MEMBRANES IN THE CANINE DUODENUM
AUTHOR: MILLER P (Reprint); POITRAS P
CORPORATE SOURCE: UNIV MONTREAL, HOP ST LUC, MONTREAL, PQ, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1996) Vol. 110, No. 4, Supp. S, pp. A1100.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 214 OF 391 MEDLINE on STN
ACCESSION NUMBER: 97078113 MEDLINE
DOCUMENT NUMBER: 97078113 PubMed ID: 8920680
TITLE: Motilin and **motilin receptor.**
AUTHOR: Satoh M; Itoh Z
CORPORATE SOURCE: Institute for Molecular and Cellular Regulation, Gunma University.
SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1996 Apr) 54 (4) 1092-6. Ref: 20
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961231

AB Motilin, a 22 amino acid polypeptide, is known to play an important role in the initiation of phase III activity of the interdigestive migrating contractions (IMC) in the dog and man. The precursor of human motilin consists of 115 amino acids including a 25 amino acid signal peptide in direct linkage with the 22 amino acid motilin sequence and a 66 amino acid carboxy-terminal motilin-associated peptide (MAP). Northern blot analysis revealed that motilin mRNA is abundant in the duodenum. In vitro studies suggested that motilin acts directly on **motilin receptors** located on gastrointestinal smooth muscle cells in the

rabbit, cat and man. On the contrary, in vivo studies suggested that **motilin receptors** are likely to be present in the nervous system. The cloning of **motilin receptors** is needed to clarify the detailed mechanism(s) of motilin's action.

L19 ANSWER 215 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:301182 BIOSIS
DOCUMENT NUMBER: PREV199699023538
TITLE: The presence and distribution of motilin and **motilin receptors** in the brain of the rabbit are suggestive for a physiological role of motilin as a neuropeptide.
AUTHOR(S): Depoortere, I.; Peeters, T. L.; De Clercq, P.; Svoboda, M.
CORPORATE SOURCE: Gut Hormone Lab., KULeuven, Leuven, Belgium
SOURCE: Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A1066. Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 2 Jul 1996

L19 ANSWER 216 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 96:336265 SCISEARCH
THE GENUINE ARTICLE: UF737
TITLE: THE PRESENCE AND DISTRIBUTION OF MOTILIN AND **MOTILIN RECEPTORS** IN THE BRAIN OR THE RABBIT ARE SUGGESTIVE FOR A PHYSIOLOGICAL-ROLE OF MOTILIN AS A NEUROPEPTIDE
AUTHOR: DEPOORTERE L (Reprint); PEETERS T L; DECLERCQ P; SVOBODA M
CORPORATE SOURCE: VUB, DEPT BIOCHEM & NUTR, BRUSSELS, BELGIUM; KATHOLIEKE UNIV LEUVEN, GUT HORMONE LAB, LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1996) Vol. 110, No. 4, Supp. S, pp. A1066.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 217 OF 391 MEDLINE on STN DUPLICATE 97
ACCESSION NUMBER: 97151246 MEDLINE
DOCUMENT NUMBER: 97151246 PubMed ID: 8997244
TITLE: Electrophysiological characterization of a motilin agonist, GM611, on rabbit duodenal smooth muscle.
AUTHOR: Yamada K; Chen S; Abdullah N A; Tanaka M; Ito Y; Inoue R
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1996 Dec) 271 (6 Pt 1) G1003-16.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19970227
Entered Medline: 19970212
AB Effects of motilin and a newly synthesized erythromycin derivative, GM611, on membrane potential and currents of rabbit duodenal smooth muscle have

been investigated by intracellular potential recording and whole cell patch-clamp technique and compared with results from contractile experiments. Motilin and GM611 (0.01-100 nM) dose dependently produced slowly sustained depolarizations (half-maximal effective dose = 0.15 and 3.9 nM for motilin and GM611, respectively) but exhibited biphasic effects on spike activities superimposed on slow waves. With small depolarizations, the number of spike discharges increased, whereas larger depolarizations markedly reduced spike amplitude. Motilin-induced (or GM611-induced) depolarization appeared to be associated with the activation of monovalent cation-selective channels, and the reduction in the spike amplitude appeared mainly to be associated with inhibition of voltage-dependent Ca2+ channels. Furthermore, data from patch-clamp experiments suggested that Ca2+ release occurred from heparin-sensitive internal stores upon stimulation of **motilin receptors** by these agonists. Possible implications of these electrophysiological effects in motilin- or GM611-induced tonic and phasic contractions have been discussed.

L19 ANSWER 218 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 97:45672 SCISEARCH
THE GENUINE ARTICLE: WA523
TITLE: Electrophysiological characterization of a motilin agonist, GM611, on rabbit duodenal smooth muscle
AUTHOR: Yamada K; Chen S; Abdullah N A; Tanaka M; Ito Y; Inoue R (Reprint)
CORPORATE SOURCE: KYUSHU UNIV, FAC MED, DEPT PHARMACOL, FUKUOKA 81282, JAPAN (Reprint); KYUSHU UNIV, FAC MED, DEPT PHARMACOL, FUKUOKA 81282, JAPAN; KYUSHU UNIV, FAC MED, DEPT INTERNAL MED 1, FUKUOKA 81282, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (DEC 1996) Vol. 34, No. 6, pp. G1003-G1016. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0193-1857.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Effects of motilin and a newly synthesized erythromycin derivative, GM611, on membrane potential and currents of rabbit duodenal smooth muscle have been investigated by intracellular potential recording and whole cell patch-clamp technique and compared with results from contractile experiments. Motilin and GM611(0.01-100 nM) dose dependently produced slowly sustained depolarizations (half-maximal effective dose = 0.15 and 3.9 nM for motilin and GM611, respectively) but exhibited biphasic effects on spike activities superimposed on slow waves. With small depolarizations, the number of spike discharges increased, whereas larger depolarizations markedly reduced spike amplitude. Motilin-induced (or GM611-induced) depolarization appeared to be associated with the activation of monovalent cation-selective channels, and the reduction in the spike amplitude appeared mainly to be associated with inhibition of voltage-dependent Ca2+ channels. Furthermore, data from patch-clamp experiments suggested that Ca2+ release occurred from heparin-sensitive internal stores upon stimulation of **motilin receptors** by these agonists. Possible implications of these electrophysiological effects in motilin- or GM611-induced tonic and phasic contractions have been discussed.

L19 ANSWER 219 OF 391 MEDLINE on STN DUPLICATE 98
ACCESSION NUMBER: 97179366 MEDLINE
DOCUMENT NUMBER: 97179366 PubMed ID: 9027652
TITLE: Effects of erythromycin in chronic idiopathic intestinal pseudo-obstruction.

AUTHOR: Minami T; Nishibayashi H; Shinomura Y; Matsuzawa Y
CORPORATE SOURCE: Second Department of Internal Medicine, Osaka University Medical School, Suita, Japan.
SOURCE: JOURNAL OF GASTROENTEROLOGY, (1996 Dec) 31 (6) 855-9. Journal code: 9430794. ISSN: 0944-1174.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970529

AB The prokinetic effects of erythromycin, a macrolide antibiotic, on the gastrointestinal tract as a **motilin receptor** agonist and its potential value for the treatment of gastrointestinal motility disorders have recently attracted interest. The effects of erythromycin on the clinical symptoms and gastrointestinal motility of patients with chronic idiopathic pseudo-obstruction have not been investigated extensively. We presented a case of chronic idiopathic intestinal pseudo-obstruction, in a 67-year-old man in whom oral erythromycin (900 mg/day) dramatically improved postprandial abdominal distention, nausea, and vomiting. Other agents with prokinetic effects on intestinal motility, i.e., cisapride, domperidone, metoclopramide, and trimebutine maleate did not have a favorable effect. Gastric emptying, measured by the sulfamethizole method; and intestinal transit, evaluated using radio-opaque markers, were markedly improved by treatment with erythromycin. Our experience suggests that the prokinetic effects of erythromycin may be of therapeutic value in chronic idiopathic intestinal pseudo-obstruction.

L19 ANSWER 220 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 96:650136 SCISEARCH
THE GENUINE ARTICLE: VE262
TITLE: MICROBIAL CONVERSION OF EM574 AND EM523, GASTROINTESTINAL MOTOR STIMULATING AGENTS
AUTHOR: FUNABASHI Y (Reprint); HAKODA S; INATOMI N; KOYAMA K; TANIDA S; HARADA S; ITOH Z; OMURA S
CORPORATE SOURCE: TAKEDA CHEM IND LTD, DIV DISCOVERY RES, 10 WADAI, TSUKUBA, IBARAKI 30042, JAPAN (Reprint); TAKEDA CHEM IND LTD, INTELLECTUAL PROPERTY DEPT, YODOGAWA KU, OSAKA 532, JAPAN; TAKEDA CHEM IND LTD, DIV PHARMACEUT RES, YODOGAWA KU, OSAKA 532, JAPAN; GUNMA UNIV, INST MOL & CELLULAR REGULAT, GI LAB, MAEBASHI, GUMMA 371, JAPAN; KITASATO INST, MINATO KU, TOKYO 108, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF ANTIBIOTICS, (AUG 1996) Vol. 49, No. 8, pp. 802-810.
ISSN: 0021-8820.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 15
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB EM574 exerts gastrointestinal motor stimulating (GMS) activity even after being converted to its metabolites P1 and P2 in dogs. These metabolites were isolated from dog liver using a series of chromatographic procedures. Their structures were determined to be the 15- and 14-hydroxyl derivatives of EM574, respectively, by spectral analysis.

Large scale preparation by microbial transformation was investigated for further evaluation of the metabolites, because the amounts obtained by oxidation with dog liver homogenate were limited. Three strains of actinomycetes, Amycolatopsis tolypophorus IFO 13151, Dactylosporangium variesporum IFO 14104 and Nocardia capreola IFO 12847, were found to have the aiming oxidative potency. HPLC analysis of the crude extracts from

these three cultures showed that the bioactive metabolites, EM574 P1 and P2 were produced. They were isolated From the culture broth with the other bioactive products EM574 P3 and P4. These bioactive products were prepared by large scale cultivation. EM574 P3 and P4 showed GMS activity comparable to that of EM574 P1 and P2.

The structures of EM574 P3 and P4 were elucidated by spectral analysis and found to be the 3''-O-demethyl derivatives of EM574 P2 and EM574, respectively. Moreover, the absolute configuration at the C14 position of P2 was determined to be R by spectral analysis of the 6-membered cyclic carbonate of EM574 P2.

L19 ANSWER 221 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:300025 BIOSIS
DOCUMENT NUMBER: PREV199699022381
TITLE: The new motilin agonist ABT-229 strongly stimulates postprandial antral motility in healthy volunteers.
AUTHOR(S): Verhagen, M. A. M. T. [Reprint author]; Samsom, M. [Reprint author]; Kroodsma, J. M.; Edmonds, A.; Smout, A. J. P. M. [Reprint author]
CORPORATE SOURCE: Gastrointestinal Motility Unit, Univ. Hosp. Utrecht, Utrecht, Netherlands
SOURCE: Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A776. Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 15 Aug 1996

L19 ANSWER 222 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:299865 BIOSIS
DOCUMENT NUMBER: PREV199699022221
TITLE: **Motilin receptor** stimulation and gastric postoperative ileus in rat.
AUTHOR(S): Plourde, V.; Trudel, L.; Poitras, P.
CORPORATE SOURCE: Hop. St.-Luc, Univ. Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A736. Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 2 Jul 1996

L19 ANSWER 223 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 96:334948 SCISEARCH
THE GENUINE ARTICLE: UF737
TITLE: **MOTILIN RECEPTOR** STIMULATION AND GASTRIC POSTOPERATIVE ILEUS IN RAT
AUTHOR: PLOURDE V (Reprint); TRUDEL L; POITRAS G
CORPORATE SOURCE: UNIV MONTREAL, HOP ST LUC, MONTREAL, PQ, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1996) Vol. 110, No. 4, Supp. S, pp. A736.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 224 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 99
ACCESSION NUMBER: 1996:299851 BIOSIS
DOCUMENT NUMBER: PREV199699022207
TITLE: The motilide ABT-229 has a higher affinity for neural than for muscular **motilin receptors.**
AUTHOR(S): Peeters, T. L.; Depoortere, I.; Van Assche, G.; Thijs, T.
CORPORATE SOURCE: Gut Hormone Lab., Univ. Leuven, Leuven, Belgium
SOURCE: Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A733. Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 2 Jul 1996

L19 ANSWER 225 OF 391 MEDLINE on STN DUPLICATE 100
ACCESSION NUMBER: 96396980 MEDLINE
DOCUMENT NUMBER: 96396980 PubMed ID: 8804083
TITLE: Heterogeneity of **motilin receptors** in the gastrointestinal tract of the rabbit.
AUTHOR: Poitras P; Miller P; Dickner M; Mao Y K; Daniel E E; St-Pierre S; Trudel L
CORPORATE SOURCE: Centre de recherche clinique Andre-Viallet, Hopital Saint-Luc, Universite de Montreal, Quebec, Canada.
SOURCE: PEPTIDES, (1996) 17 (4) 701-7.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970124

AB Motilin, a 22-amino acid peptide synthesized in endocrine cells of intestinal mucosa, stimulates GI smooth muscle contractility. To elucidate the mode of action of motilin, we attempted to determine whether **motilin receptors** are localized on nerve cells or on smooth muscle cells of the GI tract. Mucosa-free tissues from rabbit antrum and duodenum were homogenized separately with a Polytron prior to differential centrifugation to obtain synaptosome or plasma membrane-enriched fractions, as determined by the distribution of [3H]saxitoxin (SAX) binding (neural membranes) and 5' nucleotidase (5'N) activity (smooth muscle plasma membranes). Motilin binding was evaluated by the displacement of [125I]motilin by motilin (1-22) on the various membrane fractions. In the antrum, motilin binding was highly correlated with SAX binding ($r = 0.81$, $p < 0.0005$), and also significantly with 5'N activity ($r = 0.54$, $p < 0.05$). In the duodenum, motilin binding correlated significantly with 5'N activity ($r = 0.67$, $p < 0.005$), but not with SAX binding ($r = -0.11$, NS). Receptor affinity, for the motilin antagonist MOT(1-12)[CH2NH]10-11, for motilin(1-22), and for the motilin agonist erythromycin lactobionate was significantly ($p < 0.001$, $p < 0.001$, and $p < 0.05$, respectively) higher in SAX-enriched fractions from the antrum than in 5'N-enriched fractions from the duodenum. Therefore, in the rabbit: 1) **motilin receptors** appear to be predominantly located on nerve tissues in the antrum and restricted to smooth muscle cells in the duodenum, and 2) antral receptors and duodenal receptors displayed different pharmacological characteristics, probably corresponding to two specific and heterogeneous **motilin receptor** subtypes.

L19 ANSWER 226 OF 391 MEDLINE on STN DUPLICATE 101
ACCESSION NUMBER: 96374282 MEDLINE
DOCUMENT NUMBER: 96374282 PubMed ID: 8780573
TITLE: Erythromycin inhibits rabbit pyloric smooth muscle through neuronal **motilin receptors.**
AUTHOR: Parkman H P; Pagano A P; Ryan J P
CORPORATE SOURCE: Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania, USA.
CONTRACT NUMBER: 1 K08 DK02080 (NIDDK)
SOURCE: GASTROENTEROLOGY, (1996 Sep) 111 (3) 682-90.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961030

AB BACKGROUND & AIMS: Erythromycin's effect in accelerating gastric emptying is attributed primarily to increased antral contractility. The aim of this study was to characterize erythromycin's effect on pyloric muscle. METHODS: Rabbit pyloric muscle strips were studied in vitro. RESULTS: Pyloric muscle strips developed spontaneous phasic contractions with a frequency of 1.9 +/- 0.1 contractions per minute. Erythromycin and motilin had dose-dependent inhibitory effects on pyloric muscle. At the maximal effective dose (50 mumol/L), erythromycin caused cessation of spontaneous contractions for 1.8 +/- 0.2 minutes, decreasing the initial 2-minute motility index to 35% +/- 9% ($P < 0.01$) of basal. In the presence of tetrodotoxin, both erythromycin and motilin increased pyloric contractility. Motilin tachyphylaxis both in the presence or absence of tetrodotoxin abolished the effects of erythromycin. The inhibitory effect of erythromycin was decreased by NG-nitro-L-arginine methyl ester and the vasoactive intestinal peptide antagonist [4-Chloro-D-Phe6, Leu17]vasoactive intestinal peptide. CONCLUSIONS: These studies suggest that **motilin receptors** are present on both pyloric muscle and inhibitory neurons to pyloric muscle, that the primary effect of erythromycin on the pylorus is mediated by activating **motilin receptors** on inhibitory motor neurons, and that both nitric oxide and vasoactive intestinal peptide may mediate the inhibitory effect of erythromycin.

L19 ANSWER 227 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:696044 CAPLUS
DOCUMENT NUMBER: 126:26942
TITLE: Substitution of Pro3 in [Leu13]motilin affords antagonists to the GI **motilin receptor**
AUTHOR(S): Macielag, M. J.; Depoortere, I.; Florance, J. R.; Peeters, T. L.; Dharanipragada, R.; Kim-Dettelback, J.; Marvin, M. S.; Galdes, A.
CORPORATE SOURCE: Ohmeda PPD, New Providence, NJ, 07974, USA
SOURCE: Peptides: Chemistry, Structure and Biology, Proceedings of the American Peptide Symposium, 14th, Columbus, Ohio, June 18-23, 1995 (1996), Meeting Date 1995, 659-660. Editor(s): Kaumaya, Pravin T. P.; Hodges, Robert S. Mayflower Scientific: Kingswinford, UK.
CODEN: 63NTAF
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The proline residue at position 3 of [Leu13]motilin(1-14) was systematically modified in order to elucidate the physicochem. and conformational factors leading to motilin agonism and antagonism.

L19 ANSWER 228 OF 391 MEDLINE on STN DUPLICATE 102
ACCESSION NUMBER: 97006006 MEDLINE
DOCUMENT NUMBER: 97006006 PubMed ID: 8853301
TITLE: Does motilin stimulate the gastrointestinal motility of the pig? In vitro study using smooth muscle strips and dispersed muscle cells.
AUTHOR: Kitazawa T; Kikui S; Taneike T; Ohaga A
CORPORATE SOURCE: Department of Veterinary Pharmacology, Faculty of Dairy Science, Rakuno Gakuen University, Ebe Tsu, Japan.
SOURCE: GENERAL PHARMACOLOGY, (1996 Jun) 27 (4) 655-64.
Journal code: 7602417. ISSN: 0306-3623.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970115

AB To clarify the physiological role of motilin in the pig gastrointestinal (GI) tract, effect of Leu13-porcine motilin (LMT) on the contractility of GI smooth muscle was investigated in studies using isolated muscle strips and dispersed muscle cells. LMT produced no contraction in either longitudinal muscle (LM) or circular muscle (CM) of the stomach (fundus, corpus, antrum), duodenum, ileum and colon even at 1 microM. Pretreatment with LMT (1 nM-1 microM) did not potentiate the contractile response to acetylcholine (ACh) in each muscle strip. Dispersed cells from the duodenum responded to ACh in a concentration-dependent manner (EC50 = 10 pM), but not to LMT even at a high concentration (10 microM). Electrical field stimulation (EFS) caused a frequency-dependent (0.2-10 Hz) contraction of the duodenal LM that was almost completely inhibited by atropine or tetrodotoxin. EFS caused the relaxation of duodenal CM in a frequency-dependent manner (0.1-10 Hz). This relaxation was not inhibited by atropine, propranolol, phentolamine or guanethidine, indicating the involvement of noncholinergic, nonadrenergic (NCNA) nerves. NG-nitro L-arginine methylester (L-NAME, 100 microM) attenuated the EFS-induced relaxation and the inhibition at low frequency was larger than that at high frequency. L-Arginine prevented the inhibition by L-NAME but D-arginine did not. LMT (1 nM-1 microM) had no influence on EFS-induced cholinergic contraction of LM and EFS-induced NCNA relaxation of CM layer. The present in vitro studies indicate that motilin is ineffective in producing contraction and in modulating the autonomic neuroeffector transmission of the pig GI smooth muscle, and suggest that pig GI smooth muscle lacks functional **motilin receptors.**

L19 ANSWER 229 OF 391 MEDLINE on STN DUPLICATE 103
ACCESSION NUMBER: 96176934 MEDLINE
DOCUMENT NUMBER: 96176934 PubMed ID: 8601981
TITLE: Erythromycin stimulates gastric emptying after esophagectomy with gastric replacement: a randomized clinical trial.
AUTHOR: Burt M; Scott A; Williard W C; Pommier R; Yeh S; Bains M S; Turnbull A D; Fortner J G; McCormack P M; Ginsberg R J
CORPORATE SOURCE: Division of Thoracic Surgery, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1996 Mar) 111 (3) 649-54.
Journal code: 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960517
Last Updated on STN: 19960517
Entered Medline: 19960506

AB Delayed gastric emptying after esophagogastrectomy can pose a significant early postoperative problem. Because erythromycin, which stimulates the gastric antral and duodenal **motilin receptor**, has been shown to significantly increase gastric emptying in patients with diabetic gastroparesis, we decided to evaluate its effect on gastric emptying after esophagogastrectomy. METHODS: Twenty-four patients (18 men and six women, age range 41 to 79 years, median 66 years) were randomized to receive either erythromycin lactobionate (200 mg in 50 ml normal saline solution intravenously) (n = 13) or placebo (50 ml normal saline solution intravenously (n = 11) 11 days after esophagogastrectomy (with pyloric drainage procedure). After erythromycin or placebo had been infused over a 15-minute period, patients ingested a solid meal (scrambled egg with bread) labeled with technetium 99m sulfur colloid (500 microCi) over approximately 15 minutes. Dynamic images of the stomach were then acquired over 90 minutes in the supine position by gamma imaging. Results were expressed as percentage of counts retained in the stomach (percent gastric retention) over time. RESULTS: There were no side effects of erythromycin. In the placebo group, the mean percent of radiolabeled meal retained in the stomach after 90 minutes was 88%, which was significantly greater than in the erythromycin group, 37% ($p < 0.001$). In addition, analysis of covariance demonstrated that the rate of gastric emptying (slope of the line) was significantly greater in the erythromycin-treated group than in the placebo group ($p < 0.0001$). CONCLUSION: Early satiety after esophagogastrectomy may be due to delayed gastric emptying and not due to a decrease in the gastric reservoir. Intravenous erythromycin significantly improves gastric emptying in patients after esophagogastrectomy by stimulating gastric motility.

L19 ANSWER 230 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 104
ACCESSION NUMBER: 96:108895 SCISEARCH
THE GENUINE ARTICLE: TT036
TITLE: PRACTICAL RADICAL DEOXYGENATION OF ERYTHROMYCINS BY BARTON REACTION
AUTHOR: SATO T (Reprint); KOGA H; TSUZUKI K
CORPORATE SOURCE: CHUGAI PHARMACEUT CO LTD, FUJI GOTEMBA RES LABS, 1-135 KOMAKADO, GOTEMBA, SHIZUOKA, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: HETEROCYCLES, (01 JAN 1996) Vol. 42, No. 2, pp. 499-502. ISSN: 0385-5414.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS
LANGUAGE: ENGLISH
REFERENCE COUNT: 12
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Practical radical deoxygenation method of erythromycins was established. Macrolide-type **motilin receptor** agonist GM-665 (1) has been prepared using this method.

L19 ANSWER 231 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:350859 BIOSIS
DOCUMENT NUMBER: PREV199699073215
TITLE: Motilin and erythromycin do not affect the motility of rat duodenum in vivo.
AUTHOR(S): Zara, G. P.; Tarantino, A.; Bonabello, A.; Rossi, C.; Della Pepa, C.; Canaparo, R.; Eandi, M.
CORPORATE SOURCE: Ist. Farmacol. Terapia Sperimentale, Univ. Torino, Torino, Italy
SOURCE: Fundamental and Clinical Pharmacology, (1996) Vol. 10, No. 2, pp. 224.

Meeting Info.: 3rd Joint Meeting of the Societa Italiana di Farmacologia and the French Association des Pharmacologistes. Capri, Italy. May 23-26, 1996.
ISSN: 0767-3981.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1996
Last Updated on STN: 6 Aug 1996

L19 ANSWER 232 OF 391 MEDLINE on STN DUPLICATE 105
ACCESSION NUMBER: 97092347 MEDLINE
DOCUMENT NUMBER: 97092347 PubMed ID: 8938012
TITLE: Recent advances in the pharmacology of gastrointestinal prokinetics.
AUTHOR: Tonini M
CORPORATE SOURCE: Department of Internal Medicine and Therapeutics, University of Pavia, Italy.
SOURCE: PHARMACOLOGICAL RESEARCH, (1996 Apr-May) 33 (4-5) 217-26.
Ref: 126
Journal code: 8907422. ISSN: 1043-6618.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970227

AB Gastrointestinal prokinetics promote or increase the coordination of the gut wall contractions leading to enhancement of propulsive motility and, consequently, caudal displacement of luminal contents. Currently, they are considered drugs of choice for the treatment of upper gastrointestinal tract functional motor disorders such as those associated with gastrooesophageal reflux disease, chronic dyspepsia, gastroparesis (idiopathic or secondary to other diseases) and acute or chronic idiopathic intestinal pseudo-obstruction. The aim of the present review is to give an outline of the pharmacology of currently available prokinetics and of novel drugs endowed with gastrointestinal prokinetic action that require further pharmacological and/or clinical testing. The novel drugs include recent generations of benzamide and non-benzamide 5-HT4 receptor agonists, **motilin receptor** agonists, and inhibitors of nitric oxide synthase. Furthermore, based on our improved knowledge of the role of 5-HT in emesis and gastrointestinal motility, the therapeutic potential of potent mixed 5-HT4 agonists--5-HT3 antagonists in the control of cytotoxic-drug-induced emesis and associated gut motor disturbances will be discussed. Lastly, a section of this review deals with the colon as a possible target for the action of prokinetics.

L19 ANSWER 233 OF 391 MEDLINE on STN DUPLICATE 106
ACCESSION NUMBER: 96255357 MEDLINE
DOCUMENT NUMBER: 96255357 PubMed ID: 8801522
TITLE: Isolation, sequence, and bioactivity of chicken motilin.
AUTHOR: De Clercq P; Depoortere I; Macielag M; Vandermeers A; Vandermeers-Piret M C; Peeters T L
CORPORATE SOURCE: Gut Hormone Laboratory, K.U.L., Leuven, Belgium.
SOURCE: PEPTIDES, (1996) 17 (2) 203-8.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961015
Last Updated on STN: 19970203
Entered Medline: 19960930

AB Motilin was isolated from acid extracts of the small intestine of chickens by a combination of gel filtration chromatography, ion-exchange, and reverse-phase HPLC. The purification was monitored using a radioreceptor assay. The sequence of chicken motilin is FVPFFTQSDIQKMQEK-ERNKGQ. Although the six residues differing from porcine motilin (4, 7-10, and 12) are mostly in the pharmacophore of porcine motilin, the affinity of chicken motilin and of the (1-14) fragment of chicken motilin for the **motilin receptor** of rabbit antral smooth muscle is not much reduced (pKds of 8.90 and 8.45), compared with the affinity of [Nle13]porcine motilin (pKd 9.12). With smooth muscle tissue of the chicken, however, receptors could not be demonstrated with binding studies. In the tissue bath chicken motilin induced a dose-dependent tonic contraction, which was most pronounced with muscle strips prepared from chicken jejunum. This response was blocked by the Ca2+ antagonist verapamil, but atropine, TTX, L-NNA, guanethidine, prazosin, and yohimbine had no effect. The pEC50 for chicken motilin in the chicken jejunum was 7.41. Motilins from other species had lower potencies, and [Phe3, Leu13]porcine motilin, an antagonist in the rabbit, was an agonist in the chicken. The motilin agonists erythromycin A and EM-523 were almost without effect. Tested against rabbit duodenum, chicken motilin had a smaller potency than mammalian motilins. Thus, chicken motilin and the chicken **motilin receptor** differ from their mammalian counterparts.

L19 ANSWER 234 OF 391 MEDLINE on STN DUPLICATE 107
ACCESSION NUMBER: 1998050551 MEDLINE
DOCUMENT NUMBER: 98050551 PubMed ID: 9389168
TITLE: Effect of motilin on contractile activity of isolated smooth muscle of stomach.
AUTHOR: Zhou L; Wang X
CORPORATE SOURCE: Department of Physiology, CAMS, Beijing.
SOURCE: SHENG LI HSUEH PAO [ACTA PHYSIOLOGICA SINICA], (1996 Apr) 48 (2) 165-72.
Journal code: 20730130R. ISSN: 0371-0874.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980127

AB The present study was conducted to investigate the contractile effect of motilin on isolated smooth muscle cells of rat stomach. The results were as follows: (1) Motilin elicited contraction of gastric smooth muscle cells in a dose-dependent manner from 10(-11) to 10(-10) mol. (2) At concentration of 10(-10) mol, the contractile response of antral smooth muscle cells exceeded that of the body and pyrous muscle cells. (3) Anti-motilin serum could completely eliminate the stimulatory effect of motilin, which was not affected by atropine, TTX, cimetidine or loxiglumide. (4) TMB-8, an inhibitor of intracellular Ca2+ release, could also suppress completely the motilin effect. The above results suggested that the motilin effect on isolated gastric smooth muscle cells is a direct one, being mediated by highly specific **motilin receptors** in connection with the event of intracellular release of Ca2+.

L19 ANSWER 235 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:240334 BIOSIS
DOCUMENT NUMBER: PREV199698788463
TITLE: Effect of erythromycin on early delayed gastric emptying

after pylorus preserving pancreatoduodenectomy: Case report.
AUTHOR(S): Ogawa, Tetsushi; Ohwada, Susumu; Kawamura, Osamu; Izumi, Masaru; Sato, Yoshihiro; Nakamura, Seiji; Takeyoshi, Izumi; Oriuchi, Noboru; Morishita, Yasuo
CORPORATE SOURCE: Second Dep. Surgery, Gunma Univ. Sch. Med., Maebashi, Japan
SOURCE: Japanese Journal of Gastroenterology, (1996) Vol. 93, No. 2, pp. 149-154.
ISSN: 0446-6586.
DOCUMENT TYPE: Article
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 28 May 1996
Last Updated on STN: 28 May 1996

L19 ANSWER 236 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:449628 BIOSIS
DOCUMENT NUMBER: PREV199699171984
TITLE: Functional characterization of **motilin receptor** in gastrointestinal smooth muscle of chicken.
AUTHOR(S): Kitazawa, Takio [Reprint author]; Kanaya, Shizuka; Taneike, Tetsuro; Ohga, Akira
CORPORATE SOURCE: Dep. Vet. Pharmacol., Rakuno Gakuen University, Ebetsu, Hokkaido 069, Japan
SOURCE: Japanese Journal of Pharmacology, (1996) Vol. 71, No. SUPPL. 1, pp. 111P.
Meeting Info.: 69th Annual Meeting of the Japanese Pharmacological Society. Nagasaki, Japan. March 20-23, 1996.
CODEN: JJPAAZ. ISSN: 0021-5198.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 1996
Last Updated on STN: 5 Nov 1996

L19 ANSWER 237 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:449622 BIOSIS
DOCUMENT NUMBER: PREV199699171978
TITLE: Effects of **motilin receptor** agonists on gastrointestinal motility and hemodynamics in dogs.
AUTHOR(S): Nakamura, Hiroyuki [Reprint author]; Iwai, Takeshi [Reprint author]; Asano, Tadashi [Reprint author]; Yogo, Kenji [Reprint author]; Ozaki, Ken-Ichi [Reprint author]; Takanashi, Hisanori [Reprint author]; Itoh, Zen; Ohmura, Satoshi
CORPORATE SOURCE: Chugai Pharmaceutical Co. Ltd., Nagano 399-46, Japan
SOURCE: Japanese Journal of Pharmacology, (1996) Vol. 71, No. SUPPL. 1, pp. 109P.
Meeting Info.: 69th Annual Meeting of the Japanese Pharmacological Society. Nagasaki, Japan. March 20-23, 1996.
CODEN: JJPAAZ. ISSN: 0021-5198.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 1996
Last Updated on STN: 7 Oct 1996

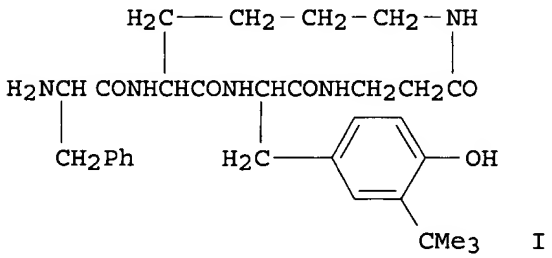
L19 ANSWER 238 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 96108880 EMBASE
DOCUMENT NUMBER: 1996108880

TITLE: [**Motilin receptors**: Gastrokinetic mechanisms].
MOTILIDES: DES GASTROKINETIQUES AUX MECANISMES.
AUTHOR: Mathis C.
CORPORATE SOURCE: INRA, Station de Recherches Porcines,35590 Saint-Gilles, France
SOURCE: Hepato-Gastro, (1996) 3/2 SUPPL. 1 (21-25).
ISSN: 1253-7020 CODEN: HEGAF6
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 048 Gastroenterology
037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: French

L19 ANSWER 239 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:781948 CAPLUS
DOCUMENT NUMBER: 123:219292
TITLE: Preparation of motilin antagonist
INVENTOR(S): Murayama, Eigoro; Haramura, Masayuki
PATENT ASSIGNEE(S): Chugai Pharmaceutical Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07138284	A2	19950530	JP 1993-338728	19931119
JP 3449766	B2	20030922		

PRIORITY APPLN. INFO.: JP 1993-338728 19931119
GI



I

AB The motilin antagonist contains (I) or its salts. **Motilin receptor** binding and contraction studies in rabbit duodenal prepns. indicated that I is a competitive motilin antagonist and can be used in motilin-related digestive disease.

L19 ANSWER 240 OF 391 MEDLINE on STN DUPLICATE 108
ACCESSION NUMBER: 96083470 MEDLINE
DOCUMENT NUMBER: 96083470 PubMed ID: 7587829
TITLE: Effect of oral erythromycin on colonic transit in patients with idiopathic constipation. A pilot study.
AUTHOR: Sharma S S; Bhargava N; Mathur S C
CORPORATE SOURCE: Department of Medicine, SMS Medical College & Hospital, Jaipur, India.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (1995 Nov) 40 (11) 2446-9.
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951228

AB Erythromycin, a **motilin receptor** agonist has been shown to have prokinetic effects on the upper gastrointestinal tract and gallbladder. Colonic effects of the drug are controversial, and it is debated whether human colon contains **motilin receptors** . In this study we evaluated the effects of erythromycin on colonic transit and stool frequency in 11 patients with idiopathic constipation over a 1-month period in an open study. The dose used was 1 g/day for two weeks followed by 500 mg/day for another two weeks. The mean (SE) total and segmental colonic transit was measured before and seven days after therapy in seven of these patients. A daily record of stool frequency was maintained in all 11 patients. Erythromycin shortened the total colonic transit from 86.2 (14.6) to 44.8 (8.99) hr ($P < 0.01$); however, segmental transit studies revealed a significant effect ($P < 0.01$) only in the right colon and rectosigmoid region. No significant side effects were observed with short-term therapy. These preliminary results suggest that erythromycin is of therapeutic value in patients with idiopathic constipation.

L19 ANSWER 241 OF 391 MEDLINE on STN DUPLICATE 109
ACCESSION NUMBER: 96124145 MEDLINE
DOCUMENT NUMBER: 96124145 PubMed ID: 8545245
TITLE: Excitatory action of [Leu13]motilin on the gastrointestinal smooth muscle isolated from the chicken.
AUTHOR: Kitazawa T; Taneike T; Ohga A
CORPORATE SOURCE: Department of Veterinary Pharmacology, Faculty of Dairy Science, Rakuno Gakuen University, Ebetsu, Japan.
SOURCE: PEPTIDES, (1995) 16 (7) 1243-52.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960227
Last Updated on STN: 19960227
Entered Medline: 19960213

AB The effects of a porcine motilin analogue, [Leu13]motilin (LMT) on the smooth muscle preparations isolated from the chicken gastrointestinal (GI) tract were investigated in vitro. In the proventriculus, LMT (100 nM to 30 microM) caused an atropine-sensitive contraction and enhanced the electrical field stimulation (EFS)- or 1,1-dimethyl-4-phenyl-piperazinium (DMPP)-induced contraction without affecting the response to acetylcholine (ACh). LMT also caused a concentration-dependent contraction of the intestinal tract (duodenum, jejunum, ileum, and colon). The responsiveness to LMT was strongest in the jejunum and weakest in the colon. The responses to LMT in the intestinal segments were not affected by tetrodotoxin, atropine, hexamethonium, pyrilamine, spantide, and 5-hydroxyltryptamine-induced desensitzation, but significantly decreased by verapamil or removal of external Ca2+. LMT did not enhance the EFS- or DMPP-induced contraction in the ileum. Canine motilin also contracted the intestinal segments in a similar concentration range to LMT with an equal potency, but erythromycin A (EMA) and N-ethyl-N-demethyl-8,9-anhydroerythromycin A, 6-9-hemiketal (EM523) showed only a weak contractile activity even at high concentration (up to 100 microM), indicating that **motilin receptors** in the chicken intestine were somewhat different from those of mammals. In conclusion, LMT produces an excitatory response in the chicken GI tract with a different sensitivity from region to region. The mechanisms of the action

were different between the proventriculus and small intestine; that is, LMT contracts the small intestine through the direct action on the smooth muscle cells, but this peptide acts on the enteric cholinergic neurones and stimulates ACh release, and thus regulates autonomic neuroeffector transmission in the proventriculus.

L19 ANSWER 242 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:281392 BIOSIS
DOCUMENT NUMBER: PREV199598295692
TITLE: Motilin is a neuropeptide: Demonstration of **motilin receptors** in the rabbit cerebellum.
AUTHOR(S): Depoortere, I.; Van Assche, G.; Peeters, T. L.
CORPORATE SOURCE: Gut Hormone Lab, Gasthuisberg O and N, Leuven, Belgium
SOURCE: Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A960. Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 1995
Last Updated on STN: 5 Jul 1995

L19 ANSWER 243 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:648312 SCISEARCH
THE GENUINE ARTICLE: QT863
TITLE: MOTILIN IS A NEUROPEPTIDE - DEMONSTRATION OF **MOTILIN RECEPTORS** IN THE RABBIT CEREBELLUM
AUTHOR: DEPOORTERE I (Reprint); VANASSCHE G; PETTERS T L
CORPORATE SOURCE: GASTHUISBERG ON, GUT HORMONE LAB, LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1995) Vol. 108, No. 4, Supp. S, pp. A960.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 244 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 110
ACCESSION NUMBER: 1995:271575 BIOSIS
DOCUMENT NUMBER: PREV199598285875
TITLE: Macrolide-type **motilin receptor** agonists: Acid-stable 12-O-methyl-8,9-anhydroerythromycin A 6,9-hemiacetals.
AUTHOR(S): Koga, Hiroshi [Reprint author]; Tsuzuki, Koichi; Sato, Tsutomu; Yogo, Kenji; Takanashi, Hisanori
CORPORATE SOURCE: Fuji-gotemba Res. Lab., Chugai Pharmaceutical Co. Ltd., 1-135 Komakado, Gotemba, Shizuoka 412, Japan
SOURCE: Bioorganic and Medicinal Chemistry Letters, (1995) Vol. 5, No. 8, pp. 835-838.
CODEN: BMCLE8. ISSN: 0960-894X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jun 1995
Last Updated on STN: 26 Jun 1995
AB Based on the acid decomposition mechanism of erythromycin A, 12-O-methyl-8,9-anhydroerythromycin A 6,9-hemiacetals were designed and synthesized. These compounds were acid stable and showed potent in vitro and in vivo motilin agonistic activities, and were thought to be promising orally active prokinetic agents.

L19 ANSWER 245 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:280344 BIOSIS
DOCUMENT NUMBER: PREV199598294644
TITLE: A novel and selective **motilin receptor** antagonist, GM-109, inhibits contractile response to GM-611, an acid-stable erythromycin A derivative, in the rabbit small intestine.
AUTHOR(S): Takanashi, H.; Yogo, K.; Ozaki, K.; Akima, M.; Koga, H.; Nabata, H.
CORPORATE SOURCE: Fuji-Gotemba Res. Lab., Chugai Pharmaceutical Co. Ltd., Shizuoka 412, Japan
SOURCE: Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A697. Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 1995
Last Updated on STN: 5 Jul 1995

L19 ANSWER 246 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:647265 SCISEARCH
THE GENUINE ARTICLE: QT863
TITLE: A NOVEL AND SELECTIVE **MOTILIN RECEPTOR** ANTAGONIST, GM-109, INHIBITS CONTRACTILE RESPONSE TO GM-611, AN ACID-STABLE ERYTHROMYCIN-A DERIVATIVE IN THE RABBIT SMALL-INTESTINE
AUTHOR: TAKANASHI H (Reprint); YOGO K; OZAKI K; AKIMA M; KOGA H; NABATA H
CORPORATE SOURCE: CHUGAI PHARMACEUT CO LTD, FUJI GOTEMBA RES LABS, SHIZUOKA 412, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: GASTROENTEROLOGY, (APR 1995) Vol. 108, No. 4, Supp. S, pp. A697.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 247 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 111
ACCESSION NUMBER: 1995:280216 BIOSIS
DOCUMENT NUMBER: PREV199598294516
TITLE: Erythromycin inhibits pyloric muscle by releasing nitric oxide and VIP through neuronal **motilin receptors.**
AUTHOR(S): Parkman, H. P. [Reprint author]; Pagano, A. P.; Ryan, J. P.
CORPORATE SOURCE: Dep. Med., Temple Univ. Sch. Med., Philadelphia, PA, USA
SOURCE: Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A665. Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 1995
Last Updated on STN: 5 Jul 1995

L19 ANSWER 248 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:280157 BIOSIS
DOCUMENT NUMBER: PREV199598294457

TITLE: Two **motilin receptor** subtypes in the gastrointestinal tract of the rabbit.
AUTHOR(S): Miller, P. [Reprint author]; Dickner, M.; Trudel, L.; Mao, Y. K.; Daniel, E. E.; St-Pierre, S.; Poitras, P.
CORPORATE SOURCE: Hop. Saint-Luc, Univ. Montreal, Montreal, PQ, Canada
SOURCE: Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A650. Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 1995
Last Updated on STN: 5 Jul 1995

L19 ANSWER 249 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:647076 SCISEARCH
THE GENUINE ARTICLE: QT863
TITLE: 2 **MOTILIN RECEPTOR** SUBTYPES IN THE GASTROINTESTINAL-TRACT OF THE RABBIT
AUTHOR: MILLER P (Reprint); DICKNER M; TRUDEL L; MAO Y K; DANIEL E E; STPIERRE S; POITRAS P
CORPORATE SOURCE: UNIV MONTREAL, HOP ST LUC, MONTREAL, PQ H3C 3J7, CANADA; MCMASTER UNIV, HAMILTON, ON L8S 4L8, CANADA; UNIV QUEBEC, INST NATL RECH SCI SANTE, MONTREAL, PQ H3C 3P8, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: GASTROENTEROLOGY, (APR 1995) Vol. 108, No. 4, Supp. S, pp. A650.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 250 OF 391 MEDLINE on STN DUPLICATE 112
ACCESSION NUMBER: 95271475 MEDLINE
DOCUMENT NUMBER: 95271475 PubMed ID: 7752063
TITLE: GM-109: a novel, selective **motilin receptor** antagonist in the smooth muscle of the rabbit small intestine.
AUTHOR: Takanashi H; Yogo K; Ozaki K; Ikuta M; Akima M; Koga H; Nabata H
CORPORATE SOURCE: Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1995 May) 273 (2) 624-8.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950629
Last Updated on STN: 19950629
Entered Medline: 19950619

AB The pharmacological properties of the cyclic peptide Phe-cyclo[Lys-Tyr(3-tBu)-beta Ala-].trifluoroacetate (GM-109), a selective motilin antagonist, were investigated in the smooth muscle of the rabbit small intestine. GM-109 (0.1-3 microM) competitively inhibited contractions induced by porcine motilin (pMTL) in rabbit isolated duodenum longitudinal strips, with a pA2 value of 7.37 +/- 0.24. However, the contractile response to acetylcholine, to substance P, to prostaglandin F2 alpha and to KCl was unaffected by 10 microM GM-109 in the same preparation. Both GM-109 and pMTL competitively inhibited 125I-pMTL binding to **motilin**

receptors in a homogenate of the rabbit small intestinal smooth muscle tissue. The pKi value of GM-109 and the pKd value of unlabeled pMTL were 7.99 +/- 0.04 and 9.25 +/- 0.06 (each n = 5), respectively. These results indicate that GM-109 is a selective and competitive **motilin receptor** antagonist in the smooth muscle of the rabbit small intestine. Thus this compound may be a useful pharmacological tool for examining the functional role(s) of motilin.

L19 ANSWER 251 OF 391 MEDLINE on STN DUPLICATE 113
ACCESSION NUMBER: 96032488 MEDLINE
DOCUMENT NUMBER: 96032488 PubMed ID: 7573453
TITLE: Gastrokinetic effects of erythromycin: myogenic and neurogenic mechanisms of action in rabbit stomach.
AUTHOR: Parkman H P; Pagano A P; Vozzelli M A; Ryan J P
CORPORATE SOURCE: Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
CONTRACT NUMBER: 1-K08-DK-02080 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1995 Sep) 269 (3 Pt 1) G418-26.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951106

AB The aims of this study were to determine regional differences and the mechanism of gastric contractile effects of erythromycin. Rabbit gastric circular muscle strips were studied in vitro. The threshold dose for erythromycin was significantly less and the maximum contraction greater in the antrum (1 microM and 0.9 +/- 0.3 kg/cm2) than in the fundus (10 microM and 0.3 +/- 0.1 kg/cm2). Erythromycin-induced antral contractions were decreased by motilin tachyphylaxis but unaffected by tetrodotoxin, atropine, hexamethonium, or ondansetron. At a subthreshold dose (0.1 microM), erythromycin increased the frequency, but not the amplitude, of bethanechol (10 +/- 3%)-and substance P-induced (13 +/- 5%) phasic antral contractions. This chronotropic effect was inhibited with tetrodotoxin, atropine, or motilin tachyphylaxis. Erythromycin (10 microM) and motilin (1 microM) enhanced the amplitude of substance P-induced tonic fundic contractions by 38 and 32%, respectively, without effect on bethanechol-induced contractions. In summary, erythromycin contracts antral muscle more potently and forcefully than fundic muscle. Erythromycin increases antral contractility by two mechanisms: an inotropic effect acting on smooth muscle **motilin receptors**, and, at lower doses, a cholinergic chronotropic effect mediated through neuronal **motilin receptors.**

L19 ANSWER 252 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:660287 SCISEARCH
THE GENUINE ARTICLE: RV401
TITLE: GASTROKINETIC EFFECTS OF ERYTHROMYCIN - MYOGENIC AND NEUROGENIC MECHANISMS OF ACTION IN RABBIT STOMACH
AUTHOR: PARKMAN H P (Reprint); PAGANO A P; VOZZELLI M A; RYAN J P
CORPORATE SOURCE: TEMPLE UNIV HOSP & MED SCH, DEPT MED, GASTROENTEROL SECT, PARKINSON PAVIL, 8TH FLOOR, 3401 N BROAD ST, PHILADELPHIA, PA, 19140 (Reprint); TEMPLE UNIV, SCH MED, DEPT MED, PHILADELPHIA, PA, 19140; TEMPLE UNIV, SCH MED, DEPT PHYSIOL, PHILADELPHIA, PA, 19140
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (SEP 1995) Vol. 32, No. 3, pp. G418-G426.
ISSN: 0193-1857.
DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The aims of this study were to determine regional differences and the mechanism of gastric contractile effects of erythromycin. Rabbit gastric circular muscle strips were studied in vitro. The threshold dose for erythromycin was significantly less and the maximum contraction greater in the antrum (1 mu M and 0.9 +/- 0.3 kg/cm(2)) than in the fundus (10 mu M and 0.3 +/- 0.1 kg/cm(2)). Erythromycin-induced antral contractions were decreased by motilin tachyphylaxis but unaffected by tetrodotoxin, atropine, hexamethonium, or ondansetron. At a subthreshold dose (0.1 mu M), erythromycin increased the frequency, but not the amplitude, of bethanechol (10 +/- 3%)- and substance P-induced (13 +/- 5%) phasic antral contractions. This chronotropic effect was inhibited with tetrodotoxin, atropine, or motilin tachyphylaxis. Erythromycin (10 mu M) and motilin (1 mu M) enhanced the amplitude of substance P-induced tonic fundic contractions by 38 and 32%, respectively, without effect on bethanechol-induced contractions. In summary, erythromycin contracts antral muscle more potently and forcefully than fundic muscle. Erythromycin increases antral contractility by two mechanisms: an inotropic effect acting on smooth muscle **motilin receptors**, and, at lower doses, a cholinergic chronotropic effect mediated through neuronal **motilin receptors.**

L19 ANSWER 253 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:246565 BIOSIS
DOCUMENT NUMBER: PREV199598260865
TITLE: Erythromycin ameliorates abnormal gallbladder contraction in diabetic autonomic neuropathy.
AUTHOR(S): Agarwal, B.; Mehta, P.; Saluja, S.; Sethuraman, K. R.
CORPORATE SOURCE: Dep. Med., St. Luke's-Roosevelt Hosp./Columbia Univ., Columbia, NY, USA
SOURCE: Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A404.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jun 1995
Last Updated on STN: 9 Jun 1995

L19 ANSWER 254 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:379627 BIOSIS
DOCUMENT NUMBER: PREV199598393927
TITLE: Different effects of erythromycin on postprandial antroduodenal motility and gastropancreatic section in humans.
AUTHOR(S): Schirra, J.; Wank, U.; Haunschmid, B.; Goeke, G.; Katschinski, M.
CORPORATE SOURCE: Dep. Gastroenterology, Univ. Hosp. Marburg, Marburg, Germany
SOURCE: Digestion, (1995) Vol. 56, No. 4, pp. 318.
Meeting Info.: XXVIIth Meeting of the European Pancreatic Club. Barcelona, Spain. June 28-July 1, 1995.
CODEN: DIGEBW. ISSN: 0012-2823.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Sep 1995
Last Updated on STN: 1 Sep 1995

L19 ANSWER 255 OF 391 MEDLINE on STN DUPLICATE 114

ACCESSION NUMBER: 96192493 MEDLINE
DOCUMENT NUMBER: 96192493 PubMed ID: 8608785
TITLE: Antagonistic properties of [Phe3,Leu13]porcine motilin.
AUTHOR: Depoortere I; Macielag M J; Galdes A; Peeters T L
CORPORATE SOURCE: Department of Pathophysiology, Katholieke Universiteit Leuven, Belgium.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1995 Nov 24) 286 (3) 241-7.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960605
Last Updated on STN: 19960605
Entered Medline: 19960528

AB We describe the antagonistic properties due to the replacement of Pro3 by phenylalanine in porcine motilin. The analogue, [Phe3,Leu13] porcine motilin (OHM-11526), displaces iodinated [Nle13]porcine motilin bound to a homogenate of rabbit antral smooth muscle tissue. The dissociation constant (pKd) was 9.26 +/- 0.04, versus 9.11 +/- 0.01 for motilin and 8.24 +/- 0.06 for ANQ-11125, the (1-14) fragment of OHM-11526. The Hill coefficient was close to one and Schild plot analysis confirmed the competitive nature of the interaction. In the tissue bath OHM-11526 was unable to induce contractions of segments of rabbit duodenum. At a concentration of 10(-6) M, OHM-11526 was unable to induce contractions of segments of rabbit duodenum. At a concentration of 10(-6) M, OHM-11526 inhibited the effect of maximally effective doses of porcine motilin and of the erythromycin derivative, EM-523, but was without effect on contractions induced by acetylcholine, substance P and serotonin. Increasing doses of OHM-11526 shifted the dose-response curves of motilin and EM-523 to the right, but caused a depression of the maximal response as well. From the motilin curves, and assuming a dual competitive and non-competitive interaction, the pA2 was 7.79 +/- 0.08, the pD'2 6.91 +/- 0.08. The EM-523 curves yielded comparable data (pA2 = 8.10 +/- 0.12 and pD'2 = 7.06 +/- 0.13). OHM-11526 also blocked the motilin responses observed with smooth muscle strips from the rabbit and human antrum. However, in a preparation of the chicken small intestine, OHM-11526 was a full agonist with a potency (pD2 = 6.84) comparable to that of porcine motilin (pD2 = 6.71). Our data confirm the interaction of motilides with the **motilin receptor.** Due to its increased affinity for the **motilin receptor**, OHM-11526 will be a valuable took for studying the physiology of motilin and the pharmacology of motilin and motilides.

L19 ANSWER 256 OF 391 MEDLINE on STN
ACCESSION NUMBER: 95281778 MEDLINE
DOCUMENT NUMBER: 95281778 PubMed ID: 7761622
TITLE: Transduction mechanism of motilin and motilides in rabbit duodenal smooth muscle.
AUTHOR: Depoortere I; Peeters T L
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: REGULATORY PEPTIDES, (1995 Feb 14) 55 (3) 227-35.
Journal code: 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950707
Last Updated on STN: 19980206
Entered Medline: 19950623

AB The present study was undertaken to explore motilin's transduction pathway

in the rabbit. Guanine nucleotides inhibited 125I-motilin binding in rabbit antral tissue and increased the dissociation of motilin from its receptor. Motilin, the motilin agonist erythromycin A enol ether (EM-201) and carbachol (taken as control) increased the production of inositol phosphates in rabbit duodenal smooth muscle strips labeled with myo-[2-3H]inositol. The effect of carbachol was blocked by atropine. Dose-response curves revealed that 50% of this effect was obtained with 3.9 nM motilin, 170 nM EM-201, 0.54 microM carbachol. Chromatographic separation of the inositol phosphate metabolites showed significant increases in the levels of [3H]inositol bisphosphate and of [3H]inositol trisphosphate. The three substances were without effect upon the metabolism of cAMP, nor did they modulate the rise in cAMP induced by GTP. We propose that motilin's transduction pathway uses a G protein that causes an increase in inositol trisphosphate which is rapidly metabolized, and which may release calcium from intracellular stores.

L19 ANSWER 257 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:243593 BIOSIS
DOCUMENT NUMBER: PREV199598257893
TITLE: GM-611, an acid-stable erythromycin A derivative, induces contractions in the rabbit small intestine via the **motilin receptor.**
AUTHOR(S): Ozaki, Ken-Ichi; Takanashi, Hisanori; Yogo, Kenji; Akima, Michitaka; Koga, Hiroshi; Nabata, Hiroyuki
CORPORATE SOURCE: Fuji-Gotemba Res. Lab., Chugai Pharmaceutical Co. Ltd., Gotemba 412, Japan
SOURCE: Japanese Journal of Pharmacology, (1995) Vol. 67, No. SUPPL. 1, pp. 191P.
Meeting Info.: 68th Annual Meeting of the Japanese Pharmacological Society. Nagoya, Japan. March 25-28, 1995.
CODEN: JJPAAZ. ISSN: 0021-5198.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jun 1995
Last Updated on STN: 9 Jun 1995

L19 ANSWER 258 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:245531 BIOSIS
DOCUMENT NUMBER: PREV199598259831
TITLE: Effects of erythromycin on basal, pentagastrin and meal gastric acid secretion in healthy volunteers.
AUTHOR(S): Landry, Vidon N.; Sogni, P.; Chauvin, J. P.; Couturier, D.
CORPORATE SOURCE: Chaussade St. Serv. D'Hepato-gastroenterol., Hop. Cochin, 27 rue Faubourg St. Jacques, 75014 Paris, France
SOURCE: Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A145.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. San Diego, California, USA. May 14-17, 1995.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jun 1995
Last Updated on STN: 9 Jun 1995

L19 ANSWER 259 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95110663 EMBASE
DOCUMENT NUMBER: 1995110663
TITLE: The medical treatment of gastroparesis.
AUTHOR: Verlinden M.
CORPORATE SOURCE: Internat. Clinical Res./Development, Janssen Research Foundation,Beerse, Belgium

SOURCE: Chinese Journal of Gastroenterology, (1995) 11/4 (66-68).
ISSN: 1013-7696 CODEN: CMHCEH
COUNTRY: Taiwan,Province of China
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The large number of digestive complaints attributed to disturbances of gastrointestinal motility have lead to the development of agents that promote prograde movement of contents through the gastrointestinal tract and therefore are called prokinetics. Prokinetic correction of deficient motor conditions can be achieved by agents that block dopamine receptors, such as metoclopramide. These drugs are not only powerful anti-emetic agents due to their interaction with dopamine receptors in the chemo-receptor-trigger zone, but they also have peripheral prokinetic properties. However, their ability to cross the blood-brain barrier has led to the occurrence of extrapyramidal side-effects. The advent of domperidone, a peripheral dopamine receptor antagonist that does not readily enter the central nervous system, virtually eliminated this problem. However, their effects are restricted to the gastroduodenal region. A new generation of prokinetic drug has arisen in the 1980's, of which cisapride is the prototype. The target receptor for cisapride is 5-HT4 receptor located on cholinergic interneurons and motorneurons of the myenteric plexus. Interaction of cisapride with the receptor leads to increased release of acetylcholine from the myenteric plexus. Moreover, this effect is observed at all levels of the gastrointestinal tract: cisapride is the first 'pan'-prokinetic. Cisapride is effective in diabetic gastroparesis, functional dyspepsia, gastroparesis associated with intestinal pseudo-obstruction, progressive systemic sclerosis, primary anorexia nervosa, and amyloidosis. Erythromycin is an agonist of **motilin receptors** located on smooth muscle cells. It has profound prokinetic effects in the gastrointestinal region. At present, erythromycin is used when gastroparesis does not respond to cisapride, domperidone, or metoclopramide. In conclusion, motility disturbances of the gastrointestinal tract cause significant morbidity in humans and are at the basis of very common disorders such as gastroparesis and dyspepsia. The first and the best studied agent is cisapride. Macrolide compounds with no antibacterial properties, but with pronounced prokinetic action in the gut are currently being developed. Their clinical usefulness has not yet been established.

L19 ANSWER 260 OF 391 MEDLINE on STN DUPLICATE 115
ACCESSION NUMBER: 95222677 MEDLINE
DOCUMENT NUMBER: 95222677 PubMed ID: 7707457
TITLE: Effects of intravenous erythromycin on antroduodenal motility in humans: non-invasive observations with real-time ultrasound.
AUTHOR: Huang C K; Chen G H; Wahn J R; Nain H M; Cheng Y P; Chang C S; Liu J H; Ho K S
CORPORATE SOURCE: Department of Internal Medicine, Taichung Veterans General Hospital, Taiwan, Republic of China.
SOURCE: KAO-HSIUNG I HSUEH KO HSUEH TSA CHIH [KAOHSIUNG JOURNAL OF MEDICAL SCIENCES], (1995 Feb) 11 (2) 62-8.
Journal code: 8603880. ISSN: 0257-5655.
PUB. COUNTRY: TAIWAN: Taiwan, Province of China
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19990129
Entered Medline: 19950510

AB Erythromycin has been shown to act on **motilin receptors** on gastrointestinal smooth muscle in vitro and to accelerate gastric emptying in normal subjects as well as in patients with diabetic mellitus. To evaluate the motor pattern that accounts for this accelerated emptying, the effects of 12.5 mg/min erythromycin vs. placebo on postprandial motility of the antroduodenum was examined with real-time ultrasound in 15 normal subjects. During 10 minutes of observation, erythromycin significantly increased forward transpyloric flow episode (1.04 +/- 0.19 vs. 0.37 +/- 0.41; $p < 0.05$), forward transpyloric flow duration (5.79 < 4.49 vs. 3.19 < 1.72 seconds; $p < 0.05$) and improved antro-pyloro-duodenal coordination (0.43 +/- 0.23 vs. 0.21 +/- 0.17; $p < 0.05$). However, no significant differences were found for gastric peristaltic cycle (22.62 +/- 3.06 vs. 23.40 +/- 2.14 seconds; $p > 0.05$), retrograde transpyloric flow episode (0.13 +/- 0.16 vs. 0.18 +/- 0.29; $p > 0.05$), and retrograde transpyloric flow duration (1.24 +/- 0.30 vs. 1.38 +/- 0.58 seconds; $p > 0.05$). We conclude that erythromycin increases episode and duration of forward transpyloric flow, and improves antro-pyloro-duodenal coordination, which may play a role in accelerating gastric emptying.

L19 ANSWER 261 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:430375 BIOSIS
DOCUMENT NUMBER: PREV199598444675
TITLE: Two **motilin receptor** subtypes in the gastrointestinal tract of the rabbit.
AUTHOR(S): Miller, P. [Reprint author]; Dickner, M.; Trudel, L.; Mao, Y. K.; Daniel, E. E.; St-Pierre, S.; Poitras, P.
CORPORATE SOURCE: Hopital Saint-Luc, Univ. Montreal, Montreal, PQ, Canada
SOURCE: Clinical and Investigative Medicine, (1995) Vol. 18, No. 4 SUPPL., pp. B47.
Meeting Info.: Annual Meeting of the Canadian Society for Clinical Investigation and the Royal College of Physicians and Surgeons of Canada. Montreal, Quebec, Canada. September 13-17, 1995.
CODEN: CNVMDL. ISSN: 0147-958X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 1995
Last Updated on STN: 3 Oct 1995

L19 ANSWER 262 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:265865 SCISEARCH
THE GENUINE ARTICLE: QR012
TITLE: GASTRIC BUT NOT DUODENAL MOTOR EFFECTS OF ORAL ERYTHROMYCIN ARE DOSE-RELATED
AUTHOR: MATHIS C; MALBERT C H (Reprint)
CORPORATE SOURCE: INRA, PORCINES STN RECH, EQUIPE FLUX DIGEST, F-35590 ST GILLES, FRANCE (Reprint); INRA, PORCINES STN RECH, EQUIPE FLUX DIGEST, F-35590 ST GILLES, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: NEUROGASTROENTEROLOGY AND MOTILITY, (MAR 1995) Vol. 7, No. 1, pp. 47-54.
ISSN: 1350-1925.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 36
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB There has been increasing interest in the potential use of erythromycin as a prokinetic agent, despite limited data on the effect of oral administration on gastrointestinal motility. We have now evaluated, in 15 conscious pigs fitted with strain gauges, the response of (i) basal gastric motility and (ii) gastric motility during inhibition with intraduodenal triglycerides infusion to increasing doses of oral erythromycin. In the basal state, erythromycin led to dose-dependent

increases in botl. the amplitude (10-30 mg kg-1) and the frequency (10-55 mg kg-1) of gastric contractions. The corpus was more responsive than the antrum, with an increase in amplitude at lower doses. The amplitude of the duodenal contractions was also improved but not in a dose-dependent manner. Gastroduodenal coordination was unchanged regardless of the dose of erythromycin. Following inhibition of gastric motility, a dose of erythromycin below 45 mg kg-1 increased both the amplitude of gastric contractions and the gastroduodenal coordination, although individual doses produced smaller increases in amplitude than in the basal state. These results suggest that erythromycin has a different mechanism of action in the stomach compared with the duodenum. The reduced effectiveness of large doses of erythromycin has important therapeutic implications.

L19 ANSWER 263 OF 391 MEDLINE on STN DUPLICATE 116
ACCESSION NUMBER: 95328382 MEDLINE
DOCUMENT NUMBER: 95328382 PubMed ID: 7604665
TITLE: Georges Brohee Prize 1994. Motilin and the enteric nervous system in the control of interdigestive and postprandial gastric motility.
AUTHOR: Tack J
CORPORATE SOURCE: Centre for Gastroenterological Research, University Hospital Gasthuisberg, Catholic University of Leuven.
SOURCE: ACTA GASTROENTEROLOGICA BELGICA, (1995 Jan-Feb) 58 (1) 21-30. Ref: 38
Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950822
Last Updated on STN: 19950822
Entered Medline: 19950809

AB The upper gastrointestinal tract displays two different functional states: the interdigestive or fasting state, and the fed state. The fasting state is characterized by a cyclical motor pattern, the migrating motor complex (MMC). The control of the MMC is incompletely understood. Plasma levels of the hormone motilin fluctuate in synchrony with MMC, but it is still controversial whether a motilin peak triggers the MMC or whether the MMC causes motilin release. We used the motilin agonistic properties of erythromycin to resolve this issue in man. Administration of a low dose of erythromycin induced a MMC which started from the gastric antrum, unaccompanied by a motilin peak. This finding argues against a release of motilin secondary to the MMC and supports our hypothesis that in man motilin peaks trigger the MMC. We observed that higher doses of erythromycin no longer induced a MMC, but stimulated antral contractility. The enteric nervous system is involved in the control of both the fasting and fed state at each level of the gastrointestinal tract. We hypothesized that the target for motilin to trigger the MMC is the enteric nervous system in the gastric antrum. Yet, no physiological data on antral enteric neurons were available. We performed the first electrophysiological study of myenteric neurons of the gastric antrum, revealing unique electrical and synaptic properties in comparison to other regions of the gastrointestinal tract. We confirmed the role of the enteric nervous system of the gastric antrum in the control of the MMC by directly demonstrating the presence of **motilin receptors** on a subpopulation of neurons. We demonstrated that endogenous and exogenous substances that stimulate (cholecystokinin, cisapride, erythromycin) or inhibit (norepinephrine, 5-hydroxytryptamine) gastric emptying all act on antral enteric neurons. These observations strongly support the hypothesis that the enteric nervous system in the gastric antrum plays a key role in the coordination of antral peristalsis and the

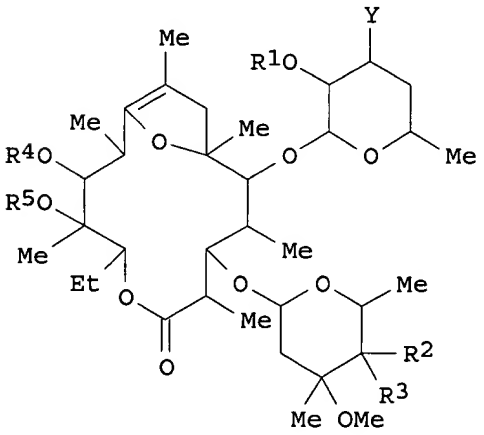
regulation of gastric emptying. Finally, we hypothesized that the actions of erythromycin on **motilin receptors** on enteric neurons and intestinal smooth muscle offer a potential for therapeutic applications in gastrointestinal motility disorders. We confirmed this by demonstrating gastrointestinal motility stimulating activity of erythromycin in patients with diabetic gastroparesis.

L19 ANSWER 264 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:297456 CAPLUS
DOCUMENT NUMBER: 122:81895
TITLE: Preparation of erythromycin derivatives
INVENTOR(S): Koga, Hiroshi; Tsuzuki, Kouichi
PATENT ASSIGNEE(S): Chugai Seiyaku K K, Japan
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9410185	A1	19940511	WO 1993-JP1594	19931104
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9453763	A1	19940524	AU 1994-53763	19931104
JP 06211886	A2	19940802	JP 1993-275543	19931104
CN 1091431	A	19940831	CN 1993-114359	19931104

PRIORITY APPLN. INFO.: JP 1992-295196 19921104
WO 1993-JP1594 19931104

OTHER SOURCE(S): MARPAT 122:81895
GI



I

AB Erythromycin derivs. [I; R1 = H or acyl; R2, R3 = H, OH, or acyloxy; or R2 and R3 may be combined together to represent O; R4 = H or lower alkyl; R5 = lower alkyl; Y = NR6R7 or N+R8R9R10.X-; R6, R7 = H, acyl, (un)substituted lower alkyl, cycloalkyl, lower alkenyl or lower alkynyl; R8, R9, R10 = H, (un)substituted lower alkyl, cycloalkyl, lower alkenyl or lower alkynyl; X- = an anion] or salts thereof are prepared I can be administered orally and show excellent effect of promoting gastrointestinal movement in mammals and improved stability against decomposition by the action of gastric juice as compared with the known

erythromycin derivs. Thus, N,2'-O-bis(benzyloxycarbonyl)-N-demethylerythromycin A was stirred with AcOH at room temperature for 1 h to give I (R1 = PhCH2O2C, R2 = OH, R3 = R4 = R5 = H, Y = NMeCO2CH2Ph) which was converted into I (R1 = R3 = H, R2 = OH, R4 = PhCH2, R5 = Me, Y = NHMe) in 4 steps. The latter compound was alkylated by iso-Pr iodide in MeOH containing (Me2CH)2NEt at 60° to give I [R1 = R3 = H, R2 = OH, R4 = PhCH2, R5 = Me, Y = NMe(iso-Pr)] which was hydrogenated over 10% Pd-C in MeOH containing CF3CO2H to give I [R1 = R3 = R4 = H, R2 = OH, R5 = Me, Y = NMe(iso-Pr)] (II). II showed IC50 of 8 + 10-9 M in DMF and 2 + 10-8 M in aqueous HCl for inhibiting the binding of 125I-labeled motilin to **motilin receptor** preparation from rabbit duodenum vs. 3 + 10-9 M in DMF and 3 + 10-7 M in aqueous HCl for the known erythromycin derivative EM-523, proving that II is more stable than EM-523 stable in aqueous HCl solution

L19 ANSWER 265 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 117
ACCESSION NUMBER: 1994:389214 BIOSIS
DOCUMENT NUMBER: PREV199497402214
TITLE: Macrolide-type **motilin receptor** agonists: Assessment of the biological value of the 2'- and 4"-hydroxyl groups of acid-stable 8,9-anhydroerythromycin A 6,9-hemiacetals.
AUTHOR(S): Koga, Hiroshi [Reprint author]; Sato, Tsutomu; Tsuzuki, Koichi; Takanashi, Hisanori
CORPORATE SOURCE: Fuji-Gotemba Res. Lab., Chugai Pharm. Co. Ltd., 1-135, Komakado, Gotemba, Shizuoka 412, Japan
SOURCE: Bioorganic and Medicinal Chemistry Letters, (1994) Vol. 4, No. 13, pp. 1649-1654.
CODEN: BMCLE8. ISSN: 0960-894X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Sep 1994
Last Updated on STN: 15 Sep 1994
AB In order to evaluate the biological significance of the 2'- and 4"-hydroxyl groups of the acid stable 11-deoxy-12-0-methyl-11-oxo-8,9-anhydroerythromycin A 6,9-hemiacetals 5-7, the 2'- and 4"-deoxy 8-11 were prepared and tested for motilin agonistic activity. It has been shown that the 4"-hydroxyl group is not a major contributor to the bioactivity, while the 2'-hydroxyl group is a mandatory one.

L19 ANSWER 266 OF 391 MEDLINE on STN
ACCESSION NUMBER: 95120376 MEDLINE
DOCUMENT NUMBER: 95120376 PubMed ID: 7820462
TITLE: Macrolides in roles beyond antibiotic therapy.
AUTHOR: Pilot M A
CORPORATE SOURCE: Surgical Unit, London Hospital Medical College, UK.
SOURCE: BRITISH JOURNAL OF SURGERY, (1994 Oct) 81 (10) 1423-9.
Ref: 107
Journal code: 0372553. ISSN: 0007-1323.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 19950223
Entered Medline: 19950216
AB Erythromycin and other macrolides with a closely related structure are widely used antibiotics. Side-effects related to administration of such drugs are mostly gastrointestinal. The direct effect of erythromycin on gastrointestinal motility was studied; it was found to have a stimulatory

effect proximally, on stomach and duodenal motility, with an apparent distal inhibition. Gastric emptying was accelerated by erythromycin via an antroduodenal coordination mechanism, an effect that has proved to be beneficial in surgical and medical conditions in which gastroparesis is a problem. Erythromycin is now used experimentally and clinically; it has been found to accelerate gastric as well as gallbladder emptying and to have an effect on the oesophagus. Analogues of erythromycin have been developed that have potent gastrointestinal activity but little or no antibacterial potential. Macrolides modulate the antibacterial action of neutrophils, with some action on the oxidative burst. Finally, two new macrolide immunosuppressants have been developed that compare favourably with traditional drugs.

L19 ANSWER 267 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 118
ACCESSION NUMBER: 1994:363227 BIOSIS
DOCUMENT NUMBER: PREV199497376227
TITLE: Potent, acid-stable and orally active macrolide-type **motilin receptor** agonists, GM-611 and the derivatives.
AUTHOR(S): Koga, Hiroshi [Reprint author]; Sato, Tsutomu; Tsuzuki, Koichi; Onoda, Harumi; Kuboniwa, Hitoshi; Takanashi, Hisanori
CORPORATE SOURCE: Fuji-Gotemba Res. Lab., Chugai Pharm. Co. Ltd., 1-135 Komakado, Gotemba, Shizuoka 412, Japan
SOURCE: Bioorganic and Medicinal Chemistry Letters, (1994) Vol. 4, No. 11, pp. 1347-1352.
CODEN: BMCLE8. ISSN: 0960-894X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Aug 1994
Last Updated on STN: 24 Aug 1994
AB Based on the acid decomposition mechanism of erythromycin A, 11-deoxy-12-O-methyl-11-oxo-8,9-anhydroerythromycin A 6,9-hemiacetals were designed and synthesized. GM-611 (11) and the derivatives 8 and 10 were acid-stable and showed potent in vitro and in vivo motilin agonistic activities, and these compounds were thought to be promising orally active prokinetic agents.

L19 ANSWER 268 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1994:286912 BIOSIS
DOCUMENT NUMBER: PREV199497299912
TITLE: Structural analysis of **motilin receptors** on rabbit and human gastric smooth muscle cell membranes.
AUTHOR(S): Satoh, M. [Reprint author]; Sakai, T. [Reprint author]; Sonobe, K. [Reprint author]; Nakajima, M. [Reprint author]; Horiuchi, R.; Itoh, Z. [Reprint author]
CORPORATE SOURCE: Gastrointestinal Res. Lab., Inst. Endocrinol., Gunma Univ., Maebashi, Japan
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A838.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 1 Jul 1994

L19 ANSWER 269 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 94:305025 SCISEARCH
THE GENUINE ARTICLE: NH909
TITLE: STRUCTURAL-ANALYSIS OF **MOTILIN RECEPTORS** ON RABBIT AND HUMAN GASTRIC SMOOTH-MUSCLE CELL-MEMBRANES

AUTHOR: SATOH M (Reprint); SAKAI T; SONOBE K; NAKAJIMA M; HORIUCHI R; ITOH Z
CORPORATE SOURCE: GUNMA UNIV, INST ENDOCRINOL, GASTROINTESTINAL RES LAB, MAEBASHI, GUNMA 371, JAPAN; GUNMA UNIV, DEPT PHARM, MAEBASHI, GUNMA 371, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: GASTROENTEROLOGY, (APR 1994) Vol. 106, No. 4, Supp. S, pp. A838.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 270 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 119
ACCESSION NUMBER: 1994:286888 BIOSIS
DOCUMENT NUMBER: PREV199497299888
TITLE: **Motilin receptor** subtypes in the rabbit, and their functional significance.
AUTHOR(S): Peeters, T. L. [Reprint author]; Depoortere, I. [Reprint author]; Macielag, M.
CORPORATE SOURCE: Gut Hormone Lab., University Leuven, Leuven, Belgium
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A832.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 1 Jul 1994

L19 ANSWER 271 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1994:286865 BIOSIS
DOCUMENT NUMBER: PREV199497299865
TITLE: Effect of antrectomy and truncal vagotomy on erythromycin induced pancreatic polypeptidase release.
AUTHOR(S): Masclee, A. A. M.; Ledeboer, M.; Gielkens, H.; Jebbink, M. C. W.; Lamers, C. B. H. W.
CORPORATE SOURCE: Dep. Gastroenterol. Hepatol., University Hosp., Leiden, Netherlands
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A826.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 18 Nov 1994

L19 ANSWER 272 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1994:286783 BIOSIS
DOCUMENT NUMBER: PREV199497299783
TITLE: ANQ-11168, a motilin antagonist in the rabbit, is an agonist of a low affinity **motilin receptor** in the chicken.
AUTHOR(S): Depoortere, I. [Reprint author]; Thijs, T. [Reprint author]; Macielag, M.; De Clercq, P.; Peeters, T. L.
CORPORATE SOURCE: Gut Hormone Lab., Univ. Leuven, Leuven, Belgium
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A806.
Meeting Info.: 95th Annual Meeting of the American

Gastroenterological Association. New Orleans, Louisiana, USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 1 Jul 1994

L19 ANSWER 273 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 94:304895 SCISEARCH
THE GENUINE ARTICLE: NH909
TITLE: ANQ-11168, A MOTILIN ANTAGONIST IN THE RABBIT, IS AN AGONIST OF A LOW-AFFINITY **MOTILIN RECEPTOR** IN THE CHICKEN
AUTHOR: DEPOORTERE I (Reprint); THIJS T; MACIELAG M; DECLERCQ P; PEETERS T L
CORPORATE SOURCE: OHMEDA CORP, PPD, NEW PROVIDENCE, NJ, 00000; CATHOLIC UNIV LEUVEN, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: USA; BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1994) Vol. 106, No. 4, Supp. S, pp. A806.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 274 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:672419 CAPLUS
DOCUMENT NUMBER: 121:272419
TITLE: Structure-activity studies of the [Leu13]motilin-(1-14) pharmacophore
AUTHOR(S): Macielag, M. J.; Marvin, M. S.; Peeters, T. L.; Dharanipragada, R.; Depoortere, I.; Florance, J. R.; Lessor, R. A.; Galdes, A.
CORPORATE SOURCE: Ohmeda PPD, New Providence, NJ, 07974, USA
SOURCE: Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp., 13th (1994), Meeting Date 1993, 681-3. Editor(s): Hodges, Robert S.; Smith, John A. ESCOM: Leiden, Neth.
CODEN: 60LXAW
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The structure-activity relationships of the Phe1, Val2, and Ile4 side chains of [Leu13]Mot-(1-14) suggest that the **motilin receptor** contains a substantial hydrophobic pocket which is capable of accommodating a wide variety of aromatic and aliphatic moieties without loss of binding affinity. The results from the study of Tyr7 replacements indicate that effective ligand-receptor interaction is dependent on a delicate balance between electronic, steric, and hydrogen bonding effects. Although dramatic increases in potency have not as yet been realized, it is clear that the design of high affinity peptide agonists to the **motilin receptor** must incorporate the following structural features: (1) a basic N-terminal amino group; (2) hydrophobic residues at positions 1, 2, and 4; and (3) π-electron d. and possible hydrogen bond donation from the side chain of residue 7.

L19 ANSWER 275 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1994:286011 BIOSIS
DOCUMENT NUMBER: PREV199497299011
TITLE: Poor function of motilin and/or **motilin receptors** may underlie absence of migrating motor activity in preterm infants.
AUTHOR(S): Jadcherla, S. R.; Berseth, C. L.

CORPORATE SOURCE: Dep. Pediatrics, Baylor Coll. Med., Houston, TX, USA
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A612.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 1 Jul 1994

L19 ANSWER 276 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 94:304123 SCISEARCH
THE GENUINE ARTICLE: NH909
TITLE: POOR FUNCTION OF MOTILIN AND OR **MOTILIN RECEPTORS** MAY UNDERLIE ABSENCE OF MIGRATING MOTOR-ACTIVITY IN PRETERM INFANTS
AUTHOR: JADCHERLA S R (Reprint); BERSETH C L
CORPORATE SOURCE: BAYLOR COLL MED, DEPT PEDIAT, HOUSTON, TX, 77030
COUNTRY OF AUTHOR: USA
SOURCE: GASTROENTEROLOGY, (APR 1994) Vol. 106, No. 4, Supp. S, pp. A612.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 277 OF 391 MEDLINE on STN DUPLICATE 120
ACCESSION NUMBER: 95221081 MEDLINE
DOCUMENT NUMBER: 95221081 PubMed ID: 7705980
TITLE: Synthesis and characterization of site-specific biotinylated probes for the **motilin receptor.**
AUTHOR: Macielag M J; Peeters T; Depoortere I
CORPORATE SOURCE: Ohmeda PPD, New Providence, New Jersey, USA.
SOURCE: INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (1994 Dec) 44 (6) 582-8.
Journal code: 0330420. ISSN: 0367-8377.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19950518
Entered Medline: 19950509

AB The solid-phase synthesis of two porcine motilin derivatives, specifically biotinylated on the side chain of Lys20, was accomplished by preactivation of the protected amino acids N alpha-(9-fluorenylmethoxycarbonyl)-N epsilon-biotinyl-L-lysine and N alpha-(9-fluorenylmethoxycarbonyl)-N epsilon-[N-(biotinyl)-6-aminohexanoyl]-L-lysine with BOP/HOBt/DIEA (1:1:2.5) followed by coupling to the support-bound peptide substrate. The biotin moiety was stable to TFA cleavage and repetitive cycles of acylation, as evidenced by the high level of purity (> 80%) of the crude peptides. This direct synthetic approach complements existing orthogonal protection strategies for the site-specific biotinylation of peptides. The derivatized peptides were purified by RP-HPLC and characterized by mass spectral and amino acid analysis. In binding studies using a rabbit antral smooth muscle homogenate, both [Leu13, Lys20 (N epsilon-biotinyl)]porcine motilin (3) and [Leu13, Lys20 (N epsilon-[N-(biotinyl)-6-aminohexanoyl])]porcine motilin (4) possessed nearly equal affinities for the **motilin receptor** (IC50 = 0.89 and 1.2 nM, respectively) as native porcine motilin (1) (IC50 =

0.76 nM). The biotinylated peptides were also highly potent in tissue bath assays employing rabbit duodenal smooth muscle segments. In contrast, commercially available [N alpha-biotinylPhe1]porcine motilin (5) had markedly lower affinity in the binding assay (IC50 = 30 nM). The relative bioactivities of these receptor probes are in accord with previous synthetic studies on motilin which demonstrated the importance of the amino-terminal segment in the high affinity interaction between the peptide and its receptor. Analog 3 retained high affinity for the **motilin receptor** in the presence of avidin. Therefore, this peptide is expected to be a valuable tool for the isolation and identification of **motilin receptors.**

L19 ANSWER 278 OF 391 MEDLINE on STN DUPLICATE 121
ACCESSION NUMBER: 95055128 MEDLINE
DOCUMENT NUMBER: 95055128 PubMed ID: 7965757
TITLE: EM574, an erythromycin derivative, is a potent **motilin receptor** agonist in human gastric antrum.
AUTHOR: Satoh M; Sakai T; Sano I; Fujikura K; Koyama H; Ohshima K; Itoh Z; Omura S
CORPORATE SOURCE: Gastrointestinal Research Laboratory, Gunma University, Maebashi, Japan.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994 Oct) 271 (1) 574-9.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19960129
Entered Medline: 19941125

AB Erythromycin and its derivatives are known to induce phase III-like contractions, which are similar to those induced by motilin, in the human gastrointestinal tract during the interdigestive state, but few detailed in vitro studies have been reported. We evaluated EM574, an erythromycin derivative, as a **motilin receptor** agonist in the human gastric antrum in vitro, using contraction studies of muscle strips and isolated myocytes, receptor binding assay and tissue section autoradiography. EM574 stimulated contractions of muscle strips in a concentration-dependent manner (10(-7)-10(-5) M), and this contractile effect was unaffected by pretreatment with atropine or tetrodotoxin. Isolated myocytes contracted in response to EM574 with a peak shortening at 10(-7) M, which was comparable to the response to motilin. EM574 displaced specifically 125I-motilin bound to smooth muscle homogenates with a Kd value of 7.8 x 10(-9) M, compared with 4.5 x 10(-9) M for motilin. Film autoradiograms showed that 125I-motilin-binding sites were localized in the muscle layers, and that the labeling disappeared in the presence of a 1000 times molar concentration of EM574. We conclude that EM574 directly stimulates smooth muscle cell contraction by acting on **motilin receptors** in the human gastric antrum in vitro.

L19 ANSWER 279 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 122
ACCESSION NUMBER: 1994:285780 BIOSIS
DOCUMENT NUMBER: PREV199497298780
TITLE: Interaction of cisapride with the **motilin receptor.**
AUTHOR(S): Peeters, T. L. [Reprint author]; Depoortere, I.; Thijs, T.; Macielag, M.; Galdes, A.
CORPORATE SOURCE: Gut Hormone Lab., Univ. Leuven, Leuven, Belgium
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A554.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana,

USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 1 Jul 1994

L19 ANSWER 280 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1994:285752 BIOSIS
DOCUMENT NUMBER: PREV199497298752
TITLE: Erythromycin derivative, A-81229: A gastrointestinal prokinetic agent.
AUTHOR(S): Nellans, H. N. [Reprint author]; Petersen, A. C.; Lartey, P. A.; Peeters, T. L.; Faghih, R.; Borre, A.; Seifert, T.; Hoffman, D.; Marsh, K.
CORPORATE SOURCE: Abbott Lab., Abbott Park, IL, USA
SOURCE: Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A547.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 15-18, 1994.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jun 1994
Last Updated on STN: 1 Jul 1994

L19 ANSWER 281 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 94:435027 SCISEARCH
THE GENUINE ARTICLE: NV407
TITLE: ISOLATED SMOOTH-MUSCLE CELLS - A TOOL TO STUDY RECEPTORS OF DIGESTIVE SMOOTH-MUSCLE
AUTHOR: DELVAUX M (Reprint)
CORPORATE SOURCE: CHU RANGUEIL, SERV GASTROENTEROL & NUTR, F-31054 TOULOUSE, FRANCE (Reprint); INRA, PHARMACOL LAB, F-31931 TOULOUSE, FRANCE; CHU RANGUEIL, SERV GASTROENTEROL & NUTR, F-31000 TOULOUSE, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: GASTROENTEROLOGIE CLINIQUE ET BIOLOGIQUE, (MAY 1994) Vol. 18, No. 5, pp. 475-485.
ISSN: 0399-8320.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 61

L19 ANSWER 282 OF 391 MEDLINE on STN DUPLICATE 123
ACCESSION NUMBER: 95091765 MEDLINE
DOCUMENT NUMBER: 95091765 PubMed ID: 7999063
TITLE: Motilin synthetic analogues and **motilin receptor** antagonists.
AUTHOR: Poitras P; Miller P; Gagnon D; St-Pierre S
CORPORATE SOURCE: Andre-Viallet Clinical Research Center, Hopital Saint-Luc, Universite de Montreal, Quebec, Canada.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1994 Nov 30) 205 (1) 449-54.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950126
Last Updated on STN: 19950126

Entered Medline: 19950117

AB While studying the structure-activity characteristics of motilin with motilin synthetic analogues, two compounds, motilin 1-12 [CH2 NH]3-4 and motilin 1-12 [CH2 NH]10-11, showed high affinity for the **motilin receptor** combined to a weak contractile activity. The following data suggest that motilin 1-12 [CH2 NH]10-11 is a potent **motilin receptor** antagonist. It showed a high affinity for the **motilin receptor** present on membranes of rabbit antrum (pIC50: 8.24 +/- 0.08 for the analogue vs 8.96 +/- 0.02 for the native peptide). When tested in vitro on strips of rabbit duodenum, the dose-response curve to motilin 1-22 was displaced to the right with motilin 1-12 [CH2 NH]10-11 (pIC50: 8.91 +/- 0.06 in presence of saline versus 7.19 +/- 0.40 with the analogue). However, when injected i.v. in dogs, motilin 1-12 [CH2 NH]10-11 was undetectable in the peripheral blood, suggesting enzymatic degradation precluding its use in vivo.

L19 ANSWER 283 OF 391 MEDLINE on STN
ACCESSION NUMBER: 95171830 MEDLINE
DOCUMENT NUMBER: 95171830 PubMed ID: 7867425
TITLE: Clinical study of erythromycin action on gallbladder motility in patients with non-ulcer dyspepsia.
AUTHOR: Liu Y G; Nie Y Q; Qian W
CORPORATE SOURCE: Union Hospital, Tongji Medical University, Wuhan.
SOURCE: CHUNG-HUA NEI KO TSA CHIH CHINESE JOURNAL OF INTERNAL MEDICINE, (1994 Jun) 33 (6) 376-8.
Journal code: 16210490R. ISSN: 0578-1426.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950407
Last Updated on STN: 19950407
Entered Medline: 19950328

AB Thirty-two patients of non-ulcer dyspepsia (NUD) with gallbladder hypokinesia treated by oral erythromycin administration 0.125g three times daily for two weeks. Before and after oral erythromycin administration, gallbladder volumes were determined by ultrasound, and plasma motilin concentration were determined by radioimmunoassay. The results showed that before and after oral erythromycin administration, maximal percentage emptying of gallbladder were 48.24 +/- 8.30ml vs 69.74 +/- 10.78ml ($P < 0.01$), plasma motilin were 361.28 +/- 87.92ng/L vs 394.97 +/- 134.27ng/L ($P > 0.05$). It is indicated that erythromycin could reduce fasting and postprandial residual gallbladder volumes and increases maximal percentage emptying of gallbladder. It suggests that erythromycin might have an agonist action on the **motilin receptor** as an agonist action on the **motilin receptor** as an exogenously administrated motilin.

L19 ANSWER 284 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 95:323342 SCISEARCH
THE GENUINE ARTICLE: QW117
TITLE: GASTROINTESTINAL MOTOR STIMULATORY EFFECTS OF KW-5139(LEU13-MOTILIN) IN THE RABBIT
AUTHOR: YOKOYAMA T (Reprint); KITAZAWA T; ICHIKAWA S; SHUTO K; ISHI A; KARASAWA A
CORPORATE SOURCE: KYOWA HAKKO KOGYO CO LTD, PHARMACEUT RES LABS, SHIZUOKA 411, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: BIOMEDICAL RESEARCH, (1994) Vol. 15, Supp. 2, pp. 309-313.
ISSN: 0388-6107.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 18

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We investigated the effects of KW-5139(Leu13-motilin) on the gastrointestinal motility in the rabbit in vitro and in vivo, and compared with those in the dog. In the dog, KW-5139 (0.3 mu g kg(-1)) evoked interdigestive migrating motor complex-like excitatory responses in vivo. In contrast to the in vivo study, the isolated duodenal strip of the dog did not show any mechanical response to KW-5139. In the anesthetized rabbits, KW-5139 (0.3-10 mu g kg(-1)) stimulated the motility of the gastric antrum, ileum, and the colon. The antrum and the colon showed relatively high sensitivity to KW-5139. Atropine (3mg kg(-1)) and naloxone (1mg kg(-1)) suppressed the motility of the gastric antrum, but only partially inhibited that of the colon. In the isolated rabbit gastrointestinal strips, KW-5139 (0.1nM-1 mu M) contracted the gastric antrum, duodenum, jejunum, ileum and the colon in concentration-dependent manners. The contractile potencies in vitro were compatible with those obtained in the present in vivo study. These results suggest that the rabbit is a useful animal to investigate motilin peptides in vivo as well as in vitro.

L19 ANSWER 285 OF 391 MEDLINE on STN
ACCESSION NUMBER: 94362030 MEDLINE
DOCUMENT NUMBER: 94362030 PubMed ID: 8080820
TITLE: New developments in macrolides: structures and antibacterial and prokinetic activities.
AUTHOR: Lartey P A; Nellans H N; Tanaka S K
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, Illinois 60064.
SOURCE: ADVANCES IN PHARMACOLOGY, (1994) 28 307-43. Ref: 184
Journal code: 9015397. ISSN: 1054-3589.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941021
Last Updated on STN: 19941021
Entered Medline: 19941013

L19 ANSWER 286 OF 391 MEDLINE on STN DUPLICATE 124
ACCESSION NUMBER: 94282464 MEDLINE
DOCUMENT NUMBER: 94282464 PubMed ID: 8012708
TITLE: Stimulating action of KW-5139 (Leu13-motilin) on gastrointestinal motility in the rabbit.
AUTHOR: Kitazawa T; Ichikawa S; Yokoyama T; Ishii A; Shuto K
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co. Ltd., Shizuoka, Japan.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1994 Jan) 111 (1) 288-94.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940810
Last Updated on STN: 19940810
Entered Medline: 19940725

AB 1. The gastrointestinal motor stimulating action of the motilin analogue, KW-5139 (Leu13-motilin), was investigated both in the anaesthetized rabbit and in rabbit isolated smooth muscle tissues. 2. KW-5139 (0.3-10 micrograms kg-1, i.v.) produced motor stimulating actions in the gastric antrum, ileum and descending colon, the excitatory responses of which were initiated at the same time but declined with different time courses. The rank order of the excitatory response was: descending colon > or = gastric

antrum >> ileum. 3. Atropine (1-3 mg kg-1, i.v.) or naloxone (1 mg kg-1, i.v.) completely suppressed the excitatory response to KW-5139 in the gastric antrum, but only partially attenuated that in the descending colon. This suggests that the mechanism of the excitatory response is different in the gastric antrum and the descending colon, and that cholinergic neural pathway is involved in the response of the gastric antrum. 4. KW-5139 (0.1 nM-1 microM) caused concentration-dependent contractions of the gastric antrum, duodenum, jejunum, ileum and the descending colon in vitro. In the rabbit intestine, the contractile response to KW-5139 was strongest in the duodenum and weakest in the ileum. 5. The contractile response to KW-5139 in the intestinal segments were not affected by tetrodotoxin, but were decreased by verapamil, or pretreatment with a high concentration of porcine motilin, confirming the involvement of **motilin receptors** in the response to KW-5139. 6. The present results suggest that the rabbit is a suitable species for the investigation of motilin on gut motility, because of the high responsiveness of the descending colon as well as the upper gastrointestinal tract.

L19 ANSWER 287 OF 391 MEDLINE on STN DUPLICATE 125
ACCESSION NUMBER: 94277856 MEDLINE
DOCUMENT NUMBER: 94277856 PubMed ID: 8008630
TITLE: Biotinyl C-terminal-extended motilin as a biologically active receptor probe.
AUTHOR: Sakai T; Satoh M; Hayashi H; Fujikura K; Sano I; Koyama H; Tatemoto K; Itoh Z
CORPORATE SOURCE: Gastrointestinal Research Laboratory, Gunma University, Maebashi, Japan.
SOURCE: PEPTIDES, (1994) 15 (2) 257-62.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940729
Last Updated on STN: 19940729
Entered Medline: 19940719

AB The synthesis, purification, and characterization of biotinylated analogues of motilin are reported. The C-terminal of canine motilin was extended by the addition of a cysteine residue, and then biotinylated. Biotinyl motilin was purified by following HPLC and characterized by amino acid analysis. Biotinylation of the ligand was confirmed by ELISA assay with the avidin-biotin system. Biotinyl motilin showed similar affinity for binding to rabbit gastric membrane fraction compared to unlabeled canine motilin, and also retained functional activity in its ability to cause contraction of rabbit duodenal segments. To determine the binding of biotinyl motilin in isolated rabbit antral smooth muscle, cells were incubated with the biotinyl motilin with and without excess of unlabeled motilin. Subsequent addition of avidin-biotinylated peroxidase complex showed the distribution of reaction products over the cell surface. Bioactive biotinyl motilin provides a useful probe for the demonstration of cell surface **motilin receptors** and will facilitate receptor purification and characterization.

L19 ANSWER 288 OF 391 MEDLINE on STN DUPLICATE 126
ACCESSION NUMBER: 95148884 MEDLINE
DOCUMENT NUMBER: 95148884 PubMed ID: 7846300
TITLE: Autoradiographic study of motilin binding sites in the rabbit gastrointestinal tract.
AUTHOR: Sakai T; Satoh M; Sonobe K; Nakajima M; Shiba Y; Itoh Z
CORPORATE SOURCE: Gastrointestinal Research Laboratory, Gunma University, Maebashi, Japan.
SOURCE: REGULATORY PEPTIDES, (1994 Oct 21) 53 (3) 249-57.
Journal code: 8100479. ISSN: 0167-0115.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950316
Last Updated on STN: 19950316
Entered Medline: 19950308

AB Although **motilin receptors** have been demonstrated by ligand binding studies, there have been no morphological studies of motilin binding site distribution. Light microscopic macro- and micro-autoradiography using highly purified iodinated Tyr23 canine motilin (10(-10) M) was carried out on the gastric antrum, duodenum, cecum and distal colon of the rabbit. Motilin binding sites were found on the smooth muscle layers of the gastric antrum, duodenum and colon, but no positive binding reaction was detected in that of the cecum. Specific binding sites were particularly abundant in the circular muscle layers, with low concentrations in the longitudinal muscle layers of the gastric antrum, duodenum and colon. No motilin binding sites were found in the mucosa of the gastrointestinal tract and pancreas. The intensity of the positive reaction was inhibited when the tissue was incubated with 10(-8) M unlabeled motilin and was completely abolished by 10(-7) M unlabeled motilin. These results are consistent with the difference in contractile response to motilin between the muscle layers of the gastrointestinal tract.

L19 ANSWER 289 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 94:187346 SCISEARCH
THE GENUINE ARTICLE: NC845
TITLE: COMPARATIVE-STUDY OF ERYTHROMYCIN, TROLEANDOMYCIN AND TYLOSIN ON THE RABBIT INTESTINE
AUTHOR: KOUNENIS G (Reprint); KOUTSOVITIPAPADOPOULOU M; ELEZOGLOU V
CORPORATE SOURCE: ARISTOTELIAN UNIV, FAC VET MED, DEPT PHARMACOL, GR-54006 THESSALONIKI, GREECE (Reprint)
COUNTRY OF AUTHOR: GREECE
SOURCE: FUNDAMENTAL & CLINICAL PHARMACOLOGY, (1994) Vol. 8, No. 2, pp. 173-177.
ISSN: 0767-3981.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 13
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The macrolide antimicrobial agents, erythromycin, troleandomycin and tylosin were tested for their effect on isolated whole segments of the rabbit duodenum, jejunum, ileum and ascending colon, as well as on strips of the circular and longitudinal smooth muscle of the ascending colon. The 14-membered macrolides erythromycin and troleandomycin were found to possess a concentration-dependent contractile effect on the intestinal smooth muscle. The order of potency was: erythromycin > troleandomycin. The 16-membered macrolide tylosin was found to have a much weaker potency than erythromycin and troleandomycin. In addition, the circular smooth muscle of the ascending colon was found to be more sensitive to the compounds tested than the longitudinal smooth muscle.

L19 ANSWER 290 OF 391 MEDLINE on STN DUPLICATE 127
ACCESSION NUMBER: 95087527 MEDLINE
DOCUMENT NUMBER: 95087527 PubMed ID: 7995205
TITLE: Mediation, muscle receptors, neurotransmitters, and drugs. Frontiers in gastric emptying.
AUTHOR: Enck P; Bueno L; Froehlich F
CORPORATE SOURCE: Department of Internal Medicine, University Hospital, Dusseldorf, Germany.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (1994 Dec) 39 (12 Suppl)

128S-129S. Ref: 12
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Conference; (CONSENSUS DEVELOPMENT CONFERENCE)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950126
Last Updated on STN: 19950126
Entered Medline: 19950117

L19 ANSWER 291 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1995:237154 BIOSIS
DOCUMENT NUMBER: PREV199598251454
TITLE: Prokinetic effects of erythromycin in preterm and term infants are related to gestational age.
AUTHOR(S): Jadcherla, Sudarshan R.; Berseth, Carol L.
CORPORATE SOURCE: Dep. Pediatrics, Baylor Coll. Med., Houston, TX, USA
SOURCE: Pediatric Research, (1994) Vol. 37, No. 4 PART 2, pp. 124A.
Meeting Info.: 105th Annual Meeting of the American Pediatric Society and the 64th Annual Meeting of the Society for Pediatric Research. San Diego, California, USA. May 7-11, 1995.
CODEN: PEREBL. ISSN: 0031-3998.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jun 1995
Last Updated on STN: 9 Jun 1995

L19 ANSWER 292 OF 391 MEDLINE on STN DUPLICATE 128
ACCESSION NUMBER: 94104313 MEDLINE
DOCUMENT NUMBER: 94104313 PubMed ID: 8277775
TITLE: Direct contractile effect of motilin on isolated smooth muscle cells from human gallbladder.
AUTHOR: Yamasaki T; Chijiiwa K; Chijiiwa Y
CORPORATE SOURCE: Department of Surgery, Kyushu University Faculty of Medicine, Fukuoka, Japan.
SOURCE: JOURNAL OF SURGICAL RESEARCH, (1994 Jan) 56 (1) 89-93.
Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940218
Last Updated on STN: 19970203
Entered Medline: 19940204

AB To test the hypothesis that **motilin receptors** are present on smooth muscle cells of the human gallbladder, smooth muscle cells were isolated from the gallbladder and their direct contractile responses to motilin were examined. Motilin elicited a dose-dependent contraction of human gallbladder smooth muscle cells. Maximal contraction rate as defined by the percentage decrease in cell length was 23.7 +/- 0.7% at 10(-7) M for motilin and was similar to that for cholecystokinin octapeptide (CCK-OP) (24.2 +/- 1.5%) observed at 10(-10) M. The contractile sensitivity of gallbladder muscle cells to motilin (ED50 = 6 pM) was two orders of magnitude less than that to CCK-OP (ED50 = 0.07 pM). The motilin-induced contraction was inhibited in a dose-dependent manner by addition of 8-(N,N-diethylamino)octyl-3,4,5-trimethoxybenzoate hydrochloride, an inhibitor of intracellular Ca2+ release. These results indicate that distinct **motilin receptors** are likely to

be present on human gallbladder smooth muscle cells, as evidenced by their direct contractile responses, and suggest that Ca2+ release from intracellular calcium stores is important in the contractile response to motilin.

L19 ANSWER 293 OF 391 MEDLINE on STN DUPLICATE 129
ACCESSION NUMBER: 95087544 MEDLINE
DOCUMENT NUMBER: 95087544 PubMed ID: 7995222
TITLE: **Motilin receptor**: a model for development of prokinetics.
AUTHOR: Peeters T L; Depoortere I
CORPORATE SOURCE: Department of Medical Research, University of Leuven, Belgium.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (1994 Dec) 39 (12 Suppl) 76S-78S.
Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950126
Last Updated on STN: 19950126
Entered Medline: 19950117

AB Erythromycin and related macrolides act as smooth muscle and neural receptors to contract rabbit duodenum and induce phase III migrating motor complex (MMC) activity in intact dogs. A recently developed motilin antagonist confirms that motility effects of erythromycin are mediated by **motilin receptors.** Despite species, organ, and tissue heterogeneity of **motilin receptors**, binding experiments with rodent antral smooth muscle tissue provide a good model for the development of this new class of prokinetics.

L19 ANSWER 294 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 130
ACCESSION NUMBER: 1994:145446 BIOSIS
DOCUMENT NUMBER: PREV199497158446
TITLE: Analysis of **motilin receptors** in canine antrum and lower esophageal sphincter myocytes.
AUTHOR(S): Petrunin, C. G.; Lardinois, C. K.; Gonzalez, R.; Starich, G. H.
CORPORATE SOURCE: Univ. Nevada Sch. Med., Veterans affairs Med. Center, Reno, NV, USA
SOURCE: Clinical Research, (1994) Vol. 42, No. 1, pp. 76A.
Meeting Info.: Joint Meeting of the Western Society for Clinical Investigation, Western Section of the American Federation for Clinical Research, Western Society for Pediatric Research, Western Region of the Society for Investigative Dermatology and the Western Student Medical Research Committee. Carmel, California, USA. February 9-12, 1994.
CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Mar 1994
Last Updated on STN: 31 Mar 1994

L19 ANSWER 295 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:345265 CAPLUS
DOCUMENT NUMBER: 122:122860
TITLE: **Motilin receptor**: a model for development of prokinetics
AUTHOR(S): Peeters, Theo L.; Depoortere, Inge
CORPORATE SOURCE: Department of Medical Research, University of Leuven,

Leuven, Belg.
SOURCE: Digestive Diseases and Sciences (1994), 39(12, Suppl.), 76S-78S
CODEN: DDSCDJ; ISSN: 0163-2116
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Erythromycin and related macrolides act at smooth muscle and neural receptors to contract rabbit duodenum and induce phase III migrating motor complex (MMC) activity in intact dogs. A recently developed motilin antagonist confirms that motility effects of erythromycin are mediated by **motilin receptors.** Despite species, organ, and tissue heterogeneity of **motilin receptors**, binding expts. with rodent antral smooth muscle tissue provide a good model for the development of this new class of prokinetics.

L19 ANSWER 296 OF 391 MEDLINE on STN DUPLICATE 131
ACCESSION NUMBER: 94023041 MEDLINE
DOCUMENT NUMBER: 94023041 PubMed ID: 8210432
TITLE: Motilide, motilin-like macrolides.
AUTHOR: Omura S; Inatomi N; Itoh Z
CORPORATE SOURCE: Kitasato Institute, Tokyo, Japan.
SOURCE: TANPAKUSHITSU KAKUSAN KOSO. PROTEIN, NUCLEIC ACID, ENZYME, (1993 Aug) 38 (11) 1881-90. Ref: 25
Journal code: 0413762. ISSN: 0039-9450.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931026

L19 ANSWER 297 OF 391 MEDLINE on STN
ACCESSION NUMBER: 94023035 MEDLINE
DOCUMENT NUMBER: 94023035 PubMed ID: 8210427
TITLE: Receptor agonists and antagonists: the present and future.
AUTHOR: Tanaka H
CORPORATE SOURCE: School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan.
SOURCE: TANPAKUSHITSU KAKUSAN KOSO. PROTEIN, NUCLEIC ACID, ENZYME, (1993 Aug) 38 (11) 1813-26. Ref: 80
Journal code: 0413762. ISSN: 0039-9450.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 20030313
Entered Medline: 19931026

L19 ANSWER 298 OF 391 MEDLINE on STN DUPLICATE 132
ACCESSION NUMBER: 94130632 MEDLINE
DOCUMENT NUMBER: 94130632 PubMed ID: 8299441
TITLE: Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis.
AUTHOR: Erbas T; Varoglu E; Erbas B; Tastekin G; Akalin S
CORPORATE SOURCE: Department of Internal Medicine, Medical Faculty, Hacettepe University, Ankara, Turkey.
SOURCE: DIABETES CARE, (1993 Nov) 16 (11) 1511-4.

Journal code: 7805975. ISSN: 0149-5992.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940318
Last Updated on STN: 19940318
Entered Medline: 19940308

AB OBJECTIVE--To compare the effects of erythromycin and metoclopramide on gastric emptying and symptoms of gastroparesis in diabetic patients with delayed gastric emptying. RESEARCH DESIGN AND METHODS--The study group consisted of 13 patients with symptoms of severe gastroparesis and delayed gastric emptying. Gastric emptying was evaluated using a radionuclide method, and gastrointestinal symptoms were scored. The patients were given either erythromycin (250 mg 3 times/day) or metoclopramide (10 mg 3 times/day) in random order for 3 wk, and after a washout period of 3 wk they were crossed-over to the other medication for another 3 wk. Parameters of gastric emptying were assessed before treatment and after both erythromycin and metoclopramide administration. RESULTS--The half-time of gastric emptying in diabetic subjects was 110 (77-120) min before treatment. At 60 and 90 min, the median value of residual isotope activity was 66.5 (55-83.5) and 55% (43-74.3), respectively. The half-time decreased to 55 min (28.6-115) after 3 wk of treatment with erythromycin and percentages of meal retention in the stomach at 60 and 90 min were 49.9 (38.4-70) and 40.5% (29.7-60), respectively. After taking metoclopramide, the median value of half-time was 67 min (15-115) and percentages of meal retention at 60 and 90 min were 51 (34.5-93.9) and 42% (24-71.2), respectively. When compared with baseline values a significant difference in gastric emptying parameters was found after both erythromycin and metoclopramide. A significant improvement of the total score for gastrointestinal symptoms was observed with both drugs, but this improvement was more pronounced with erythromycin. CONCLUSIONS--Erythromycin, a macrolide antibiotic and a **motilin receptor** agonist, appears to stimulate intestinal motility and seems to be an alternative agent for the treatment of gastroparesis caused by diabetic autonomic neuropathy.

L19 ANSWER 299 OF 391 MEDLINE on STN DUPLICATE 133
ACCESSION NUMBER: 94181469 MEDLINE
DOCUMENT NUMBER: 94181469 PubMed ID: 8134297
TITLE: Distribution and characterization of **motilin receptors** in the cat.
AUTHOR: Depoortere I; Peeters T L; Vantrappen G
CORPORATE SOURCE: Gut Hormone Lab, University of Leuven, Belgium.
SOURCE: PEPTIDES, (1993 Nov-Dec) 14 (6) 1153-7.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940428
Last Updated on STN: 19940428
Entered Medline: 19940418

AB We demonstrate binding of [125I][Nle13-po]motilin to homogenates of cat gastric and small intestinal, but not to colonic smooth muscle tissue. The density was (Bmax in fmol/mg protein): 0 (fundus); 12 +/- 2 (corpus); 22 +/- 3 (antrum); 55 +/- 12 (duodenum); 44 +/- 10 (jejunum); 17 +/- 1 (ileum); 0 (colon). A significant ($p < 0.05$) difference was found between the dissociation constant for motilin in the stomach (pKd = 8.84 +/- 0.06) and in the small intestine (pKd = 8.58 +/- 0.08). The motilides erythromycin-A (EM-A), EM-523, and EM-A N-oxide displaced labeled

[Nle13-po]motilin bound to cat duodenal receptor with potencies (pKd) of 5.47 +/- 0.23, 7.60 +/- 0.24, and < 4.3, respectively. Studies with [Leu13-po]motilin fragments showed that the N-terminus of motilin interacts with the receptor. In the tissue bath, duodenal strips mounted in the longitudinal direction responded to motilin, EM-523, and EM-A (pEC50: 8.29 +/- 0.08; 7.12 +/- 0.12; 5.99 +/- 0.15). The compounds had a comparable intrinsic activity (83 +/- 3%; 80 +/- 5%; 82 +/- 5% of the response to ACh), which was unaffected by atropine, TTX, hexamethonium, and zacopride but reduced by verapamil and calcium-free medium. Cat stomach and small intestine possess smooth muscle **motilin receptors**, which have comparable properties as those found in man and in rabbit.

L19 ANSWER 300 OF 391 MEDLINE on STN DUPLICATE 134
ACCESSION NUMBER: 94229556 MEDLINE
DOCUMENT NUMBER: 94229556 PubMed ID: 8174966
TITLE: Erythromycin induces supranormal gall bladder contraction in diabetic autonomic neuropathy.
AUTHOR: Catnach S M; Ballinger A B; Stevens M; Fairclough P D; Trembath R C; Drury P L; Watkins P J
CORPORATE SOURCE: Department of Gastroenterology, St Bartholomew's Hospital, London.
SOURCE: GUT, (1993 Aug) 34 (8) 1123-7.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940620
Last Updated on STN: 19940620
Entered Medline: 19940607

AB Gall bladder motor function is impaired in some patients with diabetes. It has been suggested that the abnormalities of gall bladder motility are confined to those patients with autonomic neuropathy. Erythromycin, a **motilin receptor** agonist, causes gall bladder contraction in both normal subjects and patients with gall stones with impaired gall bladder emptying. The effect of erythromycin on gall bladder motility in seven patients with diabetes with an autonomic neuropathy, six patients with diabetes without autonomic neuropathy, and 17 normal subjects was studied using ultrasound. There was no significant difference in gall bladder fasting volume between the three groups, but the patients with diabetes with autonomic neuropathy had impaired postprandial gall bladder emptying compared with normal subjects (percentage emptied (SEM) 40 (10.3)% v 64 (2.8)%, p < 0.01) and those with autonomic neuropathy (48 (7.7)%, NS). Erythromycin produced a dramatic reduction in gall bladder fasting volume in patients with diabetes with an autonomic neuropathy, compared with either normal subjects or patients with diabetes without autonomic neuropathy (percentage reduction 62 (4.6)% in patients with autonomic neuropathy, v 37 (17.6)% in those without autonomic neuropathy, and 26 (7.3)% in the normal subjects, (p < 0.02) and returned gall bladder emptying to normal in all patients with impaired emptying. The pronounced effect of erythromycin in diabetic autonomic neuropathy suggests denervation supersensitivity and that the action of erythromycin on the gall bladder is neurally modulated.

L19 ANSWER 301 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:503713 BIOSIS
DOCUMENT NUMBER: PREV199396127720
TITLE: Acid, motility, and ulcers: A comparison of cisapride with placebo in the prevention of duodenal ulcer relapse.
AUTHOR(S): Kerrigan, D. D. [Reprint author]; Taylor, M. E.; Read, N. W.; Johnson, A. G.

CORPORATE SOURCE: Dep. Surg., Univ. Hosp. South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR, UK
SOURCE: Gut, (1993) Vol. 34, No. 8, pp. 1042-1046.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 1993
Last Updated on STN: 6 Nov 1993

AB In a single centre double blind study of 66 patients, the value of cisapride (10 mg twice daily) was compared with placebo in the prevention of duodenal ulcer relapse. Patients who remained ulcer free attended for clinical review every two months and had a mandatory endoscopy at 0, 4, 8, and 12 months or if symptoms suggestive of ulcer recurrence developed. The 12 month crude relapse rates (that underestimate the probability of ulcer recurrence) showed that cisapride was superior to placebo (34% (11/32) relapsed on cisapride v 68% (23/34) on placebo, p=0.007). This finding was confirmed using lifetable analysis, with a 35% reduction (95% confidence intervals 10-59%, p lt 0.05) in the proportion of ulcer relapses in patients who had received cisapride compared with those treated with placebo. These results are similar to those reported in maintenance trials of H-2 receptor antagonists analysed by the same method. Drug related adverse clinical events were mainly trivial, but led to three patients on cisapride and one on placebo withdrawing from the trial.

L19 ANSWER 302 OF 391 MEDLINE on STN DUPLICATE 135
ACCESSION NUMBER: 93287003 MEDLINE
DOCUMENT NUMBER: 93287003 PubMed ID: 8510070
TITLE: Solubilization and characterization of **motilin-receptor** complexes from rabbit antral smooth muscle tissue.
AUTHOR: Depoortere I; Peeters T L; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: JOURNAL OF RECEPTOR RESEARCH, (1993) 13 (6) 903-23.
Journal code: 8008358. ISSN: 0197-5110.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930723
Last Updated on STN: 19930723
Entered Medline: 19930713

AB In the present study, the **motilin receptor** was characterized by enzymatic digestion studies and by solubilization of the **motilin-receptor** complex from prelabeled membranes using the anionic detergent cholic acid. Motilin binding was significantly decreased by preincubation of membranes of rabbit antral tissue with trypsin, phospholipase A2, C, D, dithiothreitol and 2-mercaptoethanol but not by neuraminidase and beta-galactosidase. Treatment of prelabeled membranes with 1% cholic acid resulted in solubilization of 24 +/- 5% of the proteins and 65 +/- 3% of the radioactivity. The latter was for 77 +/- 4% due to the presence of the **motilin-receptor** complex as estimated with PEG-precipitation. Upon gel-filtration on Superose 6 the complex partially dissociated but 43 +/- 3% eluted with macromolecular components in the void volume. This peak was not detected when membranes were first incubated with unlabeled motilin. Further disaggregation was accomplished by the addition of 0.5 M NaCl to the elution buffer. The chromatographic profile then showed a peak of about 370 kDa and a second one of 100 kDa. The latter value probably reflects the molecular mass of a single 125I-**motilin-receptor** -complex.

L19 ANSWER 303 OF 391 MEDLINE on STN DUPLICATE 136

ACCESSION NUMBER: 93360175 MEDLINE
DOCUMENT NUMBER: 93360175 PubMed ID: 8355213
TITLE: Down-regulation of **motilin receptors** on rabbit colon myocytes by chronic oral erythromycin.
AUTHOR: Bologna S D; Hasler W L; Owyang C
CORPORATE SOURCE: Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
CONTRACT NUMBER: MO1-RR00042 (NCRR)
P30 DK34933 (NIDDK)
RO1 DK35783 (NIDDK)
+
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1993 Aug) 266 (2) 852-6.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931008
Last Updated on STN: 19931008
Entered Medline: 19930917

AB Acutely, erythromycin stimulates colonic smooth muscle contraction via action on **motilin receptors**, but the effects of chronic erythromycin exposure are unknown. Thus contraction and motilin binding studies were performed on rabbit colonic smooth muscle after 2 weeks of oral erythromycin ethyl succinate (25 mg/kg, twice a day). Isolated colon myocytes from untreated rabbits contracted to erythromycin with an EC50 of 30 +/- 17 pM and peak shortening of 24.1 +/- 0.8% at 10 nM. Motilin evoked similar contractions with an EC50 of 63 +/- 13 pM and peak shortening of 26.8 +/- 0.9% at 10 nM. Myocytes from treated rabbits exhibited reduced contractile responses to erythromycin with an EC50 of 203 +/- 27 pM ($P < .002$) and decreased peak shortening to 20.1 +/- 2.9% at 100 nM ($P < .05$). Motilin responses were also blunted [EC50 of 326 +/- 16 pM, peak shortening of 16.2 +/- 1.2% at 1 microM ($P < .002$)]. [125I]motilin binding to untreated colon smooth muscle homogenates was saturable and specific with a Kd of 0.53 +/- 0.10 nM and a Bmax of 48 +/- 6 fmol/mg protein. Muscle from treated rabbits exhibited no change in **motilin receptor** affinity (Kd = 0.50 +/- 0.08 nM) but showed a 63% reduction in receptor density (Bmax = 18 +/- 4 fmol/mg protein; $P < .03$). In conclusion, chronic erythromycin administration results in decreased contractile potency and efficacy of motilin and erythromycin on colonic myocytes, associated with decreased **motilin receptor** density but no change in receptor affinity. Thus chronic erythromycin exposure leads to tolerance to its colonic smooth muscle motor effects via **motilin receptor** down-regulation.

L19 ANSWER 304 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:354378 BIOSIS
DOCUMENT NUMBER: PREV199345037803
TITLE: Immunohistochemical localization of motilin immunoreactive cells in the rabbit gastrointestinal tract.
AUTHOR(S): Satoh, M.; Sakai, T.; Koyama, H.; Itoh, Z.
CORPORATE SOURCE: Gastrointestinal Res. Lab., Inst. Endocrinol., Gunma University, Maebashi, Gunma 371, Japan
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A852.
Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association. Boston, Massachusetts, USA. May 15-21, 1993.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 1993
Last Updated on STN: 31 Jul 1993

L19 ANSWER 305 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:354247 BIOSIS
DOCUMENT NUMBER: PREV199345037672
TITLE: Isolation of motilin and demonstration of smooth muscle **motilin receptors** in the cat.
AUTHOR(S): Depoortere, I. [Reprint author]; Peeters, T. L. [Reprint author]; Vandermeers, A.; Vandermeers-Piret, M.-C.; Christophe, J.; Vantrappen, G. [Reprint author]
CORPORATE SOURCE: Gut Hormone Lab., K.U.L., Leuven, Belgium
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A820. Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association. Boston, Massachusetts, USA. May 15-21, 1993.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 1993
Last Updated on STN: 31 Jul 1993

L19 ANSWER 306 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 93:264243 SCISEARCH
THE GENUINE ARTICLE: KX957
TITLE: ISOLATION OF MOTILIN AND DEMONSTRATION OF SMOOTH-MUSCLE **MOTILIN RECEPTORS** IN THE CAT
AUTHOR: DEPOORTERE I (Reprint); PEETERS T L; VANDERMEERS A; VANDERMEERSPIRET M C; CHRISTOPHE J; VANTRAPPEN G
CORPORATE SOURCE: KUL, GUT HORMONE LAB, LOUVAIN, BELGIUM; ULB, CHIM BIOL LAB, BRUSSELS, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (APR 1993) Vol. 104, No. 4, Supp. S, pp. A820.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 307 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:332949 BIOSIS
DOCUMENT NUMBER: PREV199345027674
TITLE: EM574, one of the motilides acts as a motilin agonist on human stomach **motilin receptors**: In vitro demonstrations.
AUTHOR(S): Sakai, T. [Reprint author]; Satoh, M. [Reprint author]; Sano, Y. [Reprint author]; Fujikura, K. [Reprint author]; Koyama, H. [Reprint author]; Itoh, Z. [Reprint author]; Ohmura, S.
CORPORATE SOURCE: Gastrointestinal Res. Lab., Inst. Endocrinol., Gunma Univ., Maebashi 371, Japan
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A574. Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association. Boston, Massachusetts, USA. May 15-21, 1993.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 1993
Last Updated on STN: 17 Jul 1993

L19 ANSWER 308 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 93:263274 SCISEARCH
THE GENUINE ARTICLE: KX957
TITLE: EM574, ONE OF THE MOTILIDES ACTS AS A MOTILIN AGONIST ON HUMAN STOMACH **MOTILIN RECEPTORS** -

INVITRO DEMONSTRATIONS
AUTHOR: SAKAI T (Reprint); SATOH M; SANO Y; FUJIKURA K; KOYAMA H; ITOH Z; OHMURA S
CORPORATE SOURCE: GUNMA UNIV, INST ENDOCRINOL, GASTROENTEROL RES LAB, MAEBASHI, GUNMA 371, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: GASTROENTEROLOGY, (APR 1993) Vol. 104, No. 4, Supp. S, pp. A574.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 309 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:332894 BIOSIS
DOCUMENT NUMBER: PREV199345027619
TITLE: Effect of newly synthesized erythromycin derivative (EM523L) on gastric and gallbladder emptying in humans.
AUTHOR(S): Okano, H.; Aoyama, N.; Inui, A.; Miyamoto, M.; Ohmoto, A.; Nakashima, T.; Morimoto, S.; Honsako, Y.; Tamura, T.
CORPORATE SOURCE: Second Dep. Intern. Med., Kobe Univ. Sch. Med., Kobe, Japan
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A561.
Meeting Info.: 94th Annual Meeting of the American Gastroenterological Association. Boston, Massachusetts, USA. May 15-21, 1993.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jul 1993
Last Updated on STN: 17 Jul 1993

L19 ANSWER 310 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 137
ACCESSION NUMBER: 1993:351890 BIOSIS
DOCUMENT NUMBER: PREV199345035315
TITLE: Motilin: From animal to man.
AUTHOR(S): Poitras, Pierre [Reprint author]; Boivin, Michel; St-Pierre, Serge
CORPORATE SOURCE: Dep. Med., Unvi. Montreal, Cent. Recherche Clin. Andre-Viallet, Hop. St.-Luc, 1058 Rue St.-Denis, Montreal, PQ H2X 3J4, Canada
SOURCE: M-S (Medecine Sciences), (1993) Vol. 9, No. 5, pp. 547-552.
ISSN: 0767-0974.
DOCUMENT TYPE: Article
LANGUAGE: French
ENTRY DATE: Entered STN: 31 Jul 1993
Last Updated on STN: 31 Jul 1993

L19 ANSWER 311 OF 391 MEDLINE on STN DUPLICATE 138
ACCESSION NUMBER: 93228016 MEDLINE
DOCUMENT NUMBER: 93228016 PubMed ID: 8470625
TITLE: Erythromycin: a motilin agonist and gastrointestinal prokinetic agent.
AUTHOR: Weber F H Jr; Richards R D; McCallum R W
CORPORATE SOURCE: Department of Medicine, University of Virginia Health Sciences Center, Charlottesville.
SOURCE: AMERICAN JOURNAL OF GASTROENTEROLOGY, (1993 Apr) 88 (4) 485-90. Ref: 70
Journal code: 0421030. ISSN: 0002-9270.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 19930521
Entered Medline: 19930513

AB Erythromycin, a commonly used antibiotic, has recently emerged as a potential gastrointestinal prokinetic agent. This follows a decade of research into the mechanism of well-recognized gastrointestinal side effects of erythromycin. Early investigations demonstrated that erythromycin increased gastrointestinal motility, and more recent studies suggest that it fortuitously binds to and stimulates the receptor for the gastrointestinal peptide motilin. From this work it appears that a new and powerful class of gastrointestinal prokinetic agents will evolve from erythromycin and its derivatives. The role of motilin in the genesis of the fasting and fed patterns of gastrointestinal motility is emerging through the study of these motilin agonists.

L19 ANSWER 312 OF 391 MEDLINE on STN DUPLICATE 139
ACCESSION NUMBER: 93385281 MEDLINE
DOCUMENT NUMBER: 93385281 PubMed ID: 8373908
TITLE: Erythromycin increases gastric antral motility in human premature infants.
AUTHOR: Tomomasa T; Miyazaki M; Koizumi T; Kuroume T
CORPORATE SOURCE: Department of Pediatrics, Gunma University School of Medicine, Japan.
SOURCE: BIOLOGY OF THE NEONATE, (1993) 63 (6) 349-52.
Journal code: 0247551. ISSN: 0006-3126.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 19931105
Entered Medline: 19931021

AB The aim of this study was to determine if erythromycin (EM), which is a potent motilin agonist, alters gastrointestinal motility in premature infants. Six infants who were born after 23-30 weeks gestation and weighed 825-1,408 g at birth were studied when 6-31 days old. Intraluminal pressure changes within the gastric antrum and proximal duodenum were recorded. We infused EM 0.75 mg/kg intravenously for 15 min and we compared gastric and duodenal contractions for 30 min between before and after the initiation of EM infusion. In these preterm infants the migrating complex was not present, and was not induced by EM. However, in all 6 infants EM increased nonpropagating antral clusters of contractions ($p < 0.05$). The antral motility index increased 4-fold ($p < 0.05$). We concluded that human premature infants have functioning **motilin receptors.**

L19 ANSWER 313 OF 391 MEDLINE on STN DUPLICATE 140
ACCESSION NUMBER: 94091104 MEDLINE
DOCUMENT NUMBER: 94091104 PubMed ID: 8266766
TITLE: Agonist effect of erythromycin and its analogues on **motilin receptors.** A new family of prokinetics? Clinical interest.
AUTHOR: Peeters T L
CORPORATE SOURCE: Gut Hormone Laboratory, Katholieke Universiteit Leuven, Belgium.
SOURCE: ACTA GASTROENTEROLOGICA BELGICA, (1993 May-Aug) 56 (3-4) 257-60.
Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940209
Last Updated on STN: 19940209
Entered Medline: 19940121

AB It has been known since long that erythromycin may cause unpleasant gastro-intestinal side-effects such as nausea and vomiting. Recent studies however show that at low doses erythromycin may have a beneficial effect. Erythromycin induces the migrating motor complex in the fasted state and after a meal it accelerates gastric emptying. Although largely preliminary, its effects on esophageal, small intestinal, colonic and biliary tract motility have now been studied in several pathological conditions. Erythromycin is certainly a powerful gastrokinetic. Its antibiotic properties are a disadvantage, but more powerful derivatives devoid of antibacterial properties may soon become available. They form a new family of prokinetics.

L19 ANSWER 314 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 93359371 EMBASE
DOCUMENT NUMBER: 1993359371
TITLE: Motilin, erythromycin, and the gastric migrating motor complex: Site of action.
AUTHOR: Nemanich M.; Behrns K.E.; Sarr M.G.
CORPORATE SOURCE: Gastroenterology Research Unit, Mayo Clinic, 200 First Street S.W.,Rochester, MN 55905, United States
SOURCE: Journal of Gastrointestinal Motility, (1993) 5/4 (253-263). ISSN: 1043-4518 CODEN: JGMOEB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Motilin is a putative hormone which induces a premature migrating motor complex when administered exogenously, but the target organ for this hormonal effect is undetermined. Our aim was to determine whether motilin and the motilin agonist, erythromycin, induce a premature migrating motor complex via an effect directly on the stomach. Six dogs underwent splenectomy and ligation of all branches of the splenic artery except the left gastroepiploic and short gastric arteries to the proximal stomach. An intraarterial catheter was placed in the proximal splenic artery for close intra-arterial injection of motilin and erythromycin directly to the gastric corpus/proximal antrum. After recovery, the minimum effective dose required to induce a premature migrating motor complex was determined for motilin and for erythromycin given close intra-arterially or intravenously (systemically) by monitoring upper gut myoelectric activity. Minimum effective doses of motilin and erythromycin were the same whether given intra-arterially or intravenously. The latency interval or the time to onset of a premature Phase III was less than 2 minutes for intraarterial or intravenous administration ($P > 0.05$). The characteristics of induced-Phase III activity (appearance, duration, velocity) did not differ from spontaneous Phase III activity ($P > 0.05$). Although plasma motilin concentrations increased after threshold doses of both motilin and erythromycin, increases in plasma motilin occurred later after erythromycin (10 min) than after exogenous motilin (3 min). Our findings suggest that motilin initiation of the migrating motor complex does not occur by independent stimulation of putative receptors in the gastric corpus or proximal antrum.

L19 ANSWER 315 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 141
ACCESSION NUMBER: 93:726214 SCISEARCH
THE GENUINE ARTICLE: MK159
TITLE: EFFECT OF MOTILIN AND ERYTHROMYCIN ON THE MOTOR-ACTIVITY OF THE HUMAN COLON

AUTHOR: BRADETTE M; POITRAS P (Reprint); BOIVIN M
CORPORATE SOURCE: HOP ST LUC, ANDRE VIALLET CLIN RES CTR, MONTREAL H2X 3J4, PQ, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: JOURNAL OF GASTROINTESTINAL MOTILITY, (DEC 1993) Vol. 5, No. 4, pp. 247-251.
ISSN: 1043-4518.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References Keyed

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Motilin and **motilin receptor** agonist erythromycin were administered to healthy subjects where colonic motility was recorded manometrically from the hepatic flexure to the rectum. Experiments were carried out during the fasting basal state or when colonic motility was stimulated by the ingestion of a 1000 kcal lunch. A supraphysiological dose of motilin (100 ng kg(-1), i.v.) increased the motor activity of the fasting sigmoid colon, but the response was smaller than the meal induced activity. The administration of erythromycin (200 mg, i.v.) during the interdigestive period induced, on the sigmoid region, a motor response that was not significantly different in amplitude from the post-prandial contractile profile. However, on the more proximal segments of the colon, motilin and erythromycin were inactive. When both agents were administered during the digestive period, both failed to modify the contractile stimulation normally seen in all regions of the colon after a meal. Therefore the colonic motor response obtained with stimulation of **motilin receptors** in man appears limited; it is restricted to the sigmoid, it can be seen only during fasting and it is of weak amplitude.

L19 ANSWER 316 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:461824 BIOSIS
DOCUMENT NUMBER: PREV199396106724
TITLE: Aspirin (acetylsalicylic acid) effects on behavioral thermoregulation with microwave radiation.
AUTHOR(S): Vituli, William F. [Reprint author]; Laconsay, Kendra L. M.; Agnew, Andrea C.; Henderson, Mary E.; Quinn, Joseph M.; Holland, Brooke E.; Depace, Nicholas, III
CORPORATE SOURCE: PO Box U-1027, Dep. Psychol., Univ. South Alabama, Mobile, AL 36688-0001, USA
SOURCE: Perceptual and Motor Skills, (1993) Vol. 77, No. 1, pp. 187-191.
CODEN: PMOSAZ. ISSN: 0031-5125.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 1993
Last Updated on STN: 6 Oct 1993

AB Aspirin is a widely used over-the-counter drug in our society which has wide therapeutic value, yet not all of the behavioral side effects have been studied. Different doses of aspirin solutions were administered (ip) prior to fixed-interval 2-min. schedules of microwave reinforcement in rats tested in a cold environment. Four Sprague-Dawley rats were conditioned to regulate their thermal environment with 5-sec. exposures of MW reinforcement. Friedman's nonparametric test showed significant differences among aspirin and saline-control doses. Post hoc sign tests showed that a moderate dose of aspirin increased operant behavior reinforced by MW radiation, yet lower and higher doses decreased and then increased the rate of responding which resulted in an inverted U-shaped trend. Possible multiple effects of aspirin in terms of its thermoregulatory as well as its pain-tolerance properties, and implications for hypothalamic "set point" are discussed.

L19 ANSWER 317 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 142

ACCESSION NUMBER: 1993:461823 BIOSIS
DOCUMENT NUMBER: PREV199396106723
TITLE: Influence of erythromycin and terbinafine on liquid gastric emptying in healthy volunteers.
AUTHOR(S): Van Wyk, Marieta [Reprint author]; Sommers, De Klerk; Snyman, Jacques R.; Moncrieff, Joan
CORPORATE SOURCE: Dep. Pharmacology, Univ. Pretoria, P.O. Box 2034, 0001 Pretoria, South Africa
SOURCE: Current Therapeutic Research, (1993) Vol. 54, No. 2, pp. 186-190.
CODEN: CTCEA9. ISSN: 0011-393X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 1993
Last Updated on STN: 6 Oct 1993

AB This study was conducted to investigate the effects of erythromycin and terbinafine on gastric emptying of liquids in healthy volunteers, by evaluating the proportional cumulative area under the curve (PC-AUC) of paracetamol as an index of gastric emptying. Although not significant, there was a trend for erythromycin to accelerate gastric emptying. From 15 minutes onward, terbinafine reduced the PC-AUC of paracetamol significantly, indicating a delay in gastric emptying. Erythromycin, a known agonist at **motilin receptors**, generally influences gastric emptying in a dose-dependent manner; however, doses used in this study might have been insufficient to produce a significant accelerating effect on gastric emptying. This study confirms results obtained with terbinafine in rodents. Although the mechanism is still unclear, this delay is hypothesized as either an antimotilin effect or due to modulation of 5-hydroxytryptamine-stimulated acetylcholine release.

L19 ANSWER 318 OF 391 MEDLINE on STN DUPLICATE 143
ACCESSION NUMBER: 93176927 MEDLINE
DOCUMENT NUMBER: 93176927 PubMed ID: 8439638
TITLE: Dose-dependent stimulation of gallbladder contraction by intravenous erythromycin in man.
AUTHOR: Catnach S M; Ballinger A B; Law P A; Nellans H; Fairclough P D
CORPORATE SOURCE: Department of Gastroenterology, St Bartholomew's Hospital, London, UK.
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1993 Feb) 7 (1) 55-9.
Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930416
Last Updated on STN: 19930416
Entered Medline: 19930401

AB We have previously shown that a single oral dose of 500 mg erythromycin causes gallbladder contraction. The effect of intravenous erythromycin on antroduodenal motility is dose-dependent; < 3 mg/kg body weight stimulates propagated contractions in a fashion similar to motilin while doses > 7 mg/kg cause giant non-propagated antral contractions not seen with motilin. Using ultrasound, we have examined the effect of differing doses of intravenous erythromycin on gallbladder motility in man. Erythromycin (1 mg/kg) caused fasting gallbladder contraction to 52% of basal gallbladder volume ($P < 0.001$), and increased gallbladder emptying following a liquid meal (maximal percentage emptied 75 +/- 6.8% vs. 58 +/- 9.0% following saline, $P < 0.05$). Erythromycin (7 mg/kg) however, had no effect on gallbladder fasting or post-prandial motor activity. We conclude that the effect of erythromycin on gallbladder motility is dose-dependent, with higher doses having no effect. It is possible that at higher doses erythromycin stimulates other receptors in addition to the

motilin receptor, and that the combined effect is different to the stimulation of the **motilin receptor** alone.

L19 ANSWER 319 OF 391 MEDLINE on STN DUPLICATE 144
ACCESSION NUMBER: 92267311 MEDLINE
DOCUMENT NUMBER: 92267311 PubMed ID: 1587426
TITLE: Effect of oral erythromycin on gallbladder motility in normal subjects and subjects with gallstones.
COMMENT: Comment in: Gastroenterology. 1992 Dec;103(6):1995-6
Comment in: Gastroenterology. 1993 Nov;105(5):1589-90
AUTHOR: Catnach S M; Fairclough P D; Trembath R C; O'Donnell L J; McLean A M; Law P A; Wickham J E
CORPORATE SOURCE: Department of Gastroenterology, St. Bartholomew's Hospital, West Smithfield, London, England.
SOURCE: GASTROENTEROLOGY, (1992 Jun) 102 (6) 2071-6.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 19960129
Entered Medline: 19920619

AB The action of the **motilin receptor** agonist erythromycin on human gallbladder contraction, measured by ultrasound, both in normal subjects and those with gallstone disease was studied. In 17 normal subjects, oral erythromycin administration (500 mg; vs. placebo) reduced fasting gallbladder volume at 2 hours (26.2 vs. 19.0 mL; P less than 0.001), and postprandial residual gallbladder volume (9.0 vs. 4.4 mL; P less than 0.001) and the rate constant of gallbladder emptying following the meal was significantly increased. Erythromycin also reduced fasting and residual gallbladder volumes in 13 patients with gallstone disease: in 6 who underwent cholecystolithotomy, fasting volume was 29.5 vs. 22.3 mL (P less than 0.05) and residual volume was 17.7 vs. 6.5 mL (P less than 0.05), and in 7 with gallstones in situ, fasting volume was 23.8 vs. 14.3 mL (P less than 0.05) and residual volume was 17.2 vs. 5.0 mL (P less than 0.05). In 7 of 8 subjects with gallstones and impaired gallbladder emptying, the gallbladder emptied normally following administration of erythromycin, and in 3 of the other 5 gallstone subjects gallbladder emptying was increased. In 6 normal subjects given erythromycin three times weekly for 1 month, the effect was maintained (fasting volume, 18.8 mL, P less than 0.001; residual volume, 3.7 mL, P less than 0.001). Oral erythromycin significantly reduces fasting and postprandial residual gallbladder volumes in both normal subjects and subjects with gallstones and reverses the gallbladder motility defect found in a proportion of subjects with gallstones. This effect is maintained for a month in normal subjects.

L19 ANSWER 320 OF 391 MEDLINE on STN DUPLICATE 145
ACCESSION NUMBER: 93208695 MEDLINE
DOCUMENT NUMBER: 93208695 PubMed ID: 1296862
TITLE: Motilin and the postprandial motility of the antrum.
AUTHOR: Boivin M; Riberdy M; Raymond M C; Trudel L; Poitras P
CORPORATE SOURCE: Andre-Viallet Clinical Research Center, Hopital St-Luc, Universite de Montreal, Que, Canada.
SOURCE: CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1992 Nov) 70 (11) 1491-5.
Journal code: 0372712. ISSN: 0008-4212.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930514
Last Updated on STN: 19930514
Entered Medline: 19930423

AB This study was designed to establish whether the rise in plasma motilin observed after a meal in humans can influence the postprandial motor activity of the antrum. Antroduodenal postprandial motility profiles and indices obtained from 5 controls and 5 subjects infused with exogenous synthetic motilin (0.1 microgram.kg-1) or with the **motilin receptor** agonist erythromycin lactobionate (200 mg) were compared. Motilin infusion increased plasma motilin concentrations about 5 times above the physiological range but failed to modify the normal postprandial contractile response. On the other hand, in 4 of the 5 subjects, erythromycin induced an intense motor response that mimicked phase III of the migrating motor complex. Our study demonstrates that, during the postprandial period, motilin antral receptors can be stimulated only with doses of motilin exceeding the physiological plasma concentrations, and that the motor effect obtained did not mimic the usual postprandial motility pattern. Our results, therefore, do not support the proposal that the postprandial motility of the antrum is regulated by the plasma levels of motilin.

L19 ANSWER 321 OF 391 MEDLINE on STN DUPLICATE 146
ACCESSION NUMBER: 93157155 MEDLINE
DOCUMENT NUMBER: 93157155 PubMed ID: 1494493
TITLE: D-amino acid and alanine scans of the bioactive portion of porcine motilin.
AUTHOR: Peeters T L; Macielag M J; Depoortere I; Konteatis Z D; Florance J R; Lessor R A; Galdes A
CORPORATE SOURCE: Gut Hormone Lab, University of Leuven, Gasthuisberg, Belgium.
SOURCE: PEPTIDES, (1992 Nov-Dec) 13 (6) 1103-7.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930326
Last Updated on STN: 19950206
Entered Medline: 19930309

AB A recent systematic study of porcine motilin fragments has clearly shown that biological activity resides in the amino-terminal end. The amino-terminal tetradecapeptide retains more than 90% of the potency of the full molecule. We now examined the effect of replacement of residues 1 through 11 by either their D-isomer or by alanine in [Leu13]pMOT(1-14). Peptides were synthesized using Fmoc solid phase methodology, purified by HPLC, and assayed for their ability to displace bound motilin (rabbit antral smooth muscle homogenate) and to induce contractions (isolated rabbit duodenal segments). The negative logarithm of the concentration displacing 50% of the tracer (pIC50), or producing 50% of the maximal contractile response (pEC50), was determined. All compounds were still full agonists. A reduction in potency of more than two log units was seen for the compounds in which residues 1 (Phe), 4 (Ile), and 7 (Tyr) were replaced by Ala and residues 3 (Pro), 4 (Ile), and 6 (Thr) by their D-isomer. The largest drop was noted for the analogs substituted at position 4. For all compounds there was an almost perfect correlation between the pIC50 and the pEC50 values (r = 0.96), although the pEC50 was consistently smaller. These results show that the biological activity of motilin is mainly determined by the first seven residues. The pharmacophore consists of the aromatic rings from Phe1 and Tyr7 and the aliphatic side chains from Val2 and Ile4. Pro3, Phe5, and Thr6 may stabilize the bioactive conformation.

L19 ANSWER 322 OF 391 MEDLINE on STN DUPLICATE 147
ACCESSION NUMBER: 92165010 MEDLINE
DOCUMENT NUMBER: 92165010 PubMed ID: 1537520
TITLE: Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination.
AUTHOR: Annese V; Janssens J; Vantrappen G; Tack J; Peeters T L; Willemse P; Van Cutsem E
CORPORATE SOURCE: Department of Internal Medicine, University Hospital Gasthuisberg, University of Leuven, Belgium.
SOURCE: GASTROENTEROLOGY, (1992 Mar) 102 (3) 823-8.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920417
Last Updated on STN: 19960129
Entered Medline: 19920402

AB Erythromycin has been shown to act as a motilin agonist by binding to **motilin receptors** on gastrointestinal smooth muscle and to improve the severely impaired gastric emptying in patients with diabetic gastroparesis. To elucidate the motor pattern that accounts for this accelerated emptying, the effect of 200 mg erythromycin vs. placebo on postprandial motility of the stomach and the upper small intestine was examined in 13 normal subjects. Erythromycin significantly increased the amplitude of the antral contractions during the 2-hour postprandial study period (maximal difference in mean amplitude of distal antral contractions between erythromycin and placebo recorded from 80 to 90 minutes after meal: 123 +/- 17 vs. 44 +/- 12 mm Hg; P less than 0.005). The total number of antral contractions was not affected, but the contractions could be recorded manometrically higher up in the stomach after erythromycin than after placebo (9-12 vs. 3-6 cm above the pylorus). Antroduodenal coordination was significantly improved during the first postprandial hour, and the first normal phase 3 of the migrating motor complex, indicating the reappearance of fasting motility, occurred earlier after erythromycin than after placebo (128.3 +/- 14.3 vs. 173.4 +/- 16.1 minutes; P less than 0.05). These changes in postprandial motility induced by erythromycin may well account for its accelerating effect on gastric emptying.

L19 ANSWER 323 OF 391 MEDLINE on STN DUPLICATE 148
ACCESSION NUMBER: 93042499 MEDLINE
DOCUMENT NUMBER: 93042499 PubMed ID: 1420750
TITLE: Oral or intravenous erythromycin has no effect on human distal colonic motility.
AUTHOR: Jameson J S; Rogers J; Misiewicz J J; Raimundo A H; Henry M M
CORPORATE SOURCE: Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London, UK.
SOURCE: ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1992 Oct) 6 (5) 589-95.
Journal code: 8707234. ISSN: 0269-2813.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122

Entered Medline: 19921218

AB Erythromycin is a prokinetic agent for the lower oesophageal sphincter, the stomach, the gallbladder and the small bowel, acting directly on **motilin receptors.** Its effect on pressure activity of the human colon has not been investigated. Eight healthy volunteers were studied on 2 occasions and given intravenous or oral erythromycin, or placebo in a single-blind, randomized crossover study. Sigmoid pressure activity was measured using a 4-lumen water perfused system placed sigmoidoscopically at 50, 45, 30 and 15 cm from the anal verge. The pressures were analysed for activity index (mmHg.min) for the 35 cm colonic study segment using dedicated software. No significant difference was found in the activity index following oral erythromycin (500 mg) or placebo, or following intravenous erythromycin 1.8 mg/kg or placebo. A further 8 subjects were studied in a single-blind crossover study to determine the effect of oral erythromycin (500 mg) b.d. on colonic transit, measured with radio-opaque markers and a single abdominal X-ray. Mean or segmental colonic transit times were not statistically significantly different (Student's paired t-test) in the subjects on placebo or erythromycin. This lack of effect of erythromycin on the distal large intestine may indicate the absence of receptors for motilin in that part of the gut.

L19 ANSWER 324 OF 391 MEDLINE on STN DUPLICATE 149
ACCESSION NUMBER: 92396611 MEDLINE
DOCUMENT NUMBER: 92396611 PubMed ID: 1523168
TITLE: Synthesis and in vitro evaluation of [Leu13]porcine motilin fragments.
AUTHOR: Macielag M J; Peeters T L; Konteatis Z D; Florance J R; Depoortere I; Lessor R A; Bare L A; Cheng Y S; Galdes A
CORPORATE SOURCE: Boc Group Technical Center, Health Care Research, New Providence, NJ 07974.
SOURCE: PEPTIDES, (1992 May-Jun) 13 (3) 565-9.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19921023
Last Updated on STN: 19921023
Entered Medline: 19921014

AB Several peptide fragments representing N-terminal, C-terminal, and internal sequences of [Leu13]porcine motilin ([Leu13]pMOT) were synthesized using Fmoc solid phase methodology. Peptides were assayed for **motilin receptor** binding activity in a rabbit antrum smooth muscle preparation and for stimulation of contractile activity in segments of rabbit duodenum. In vitro activity was directly correlated with **motilin receptor** binding affinity for all [Leu13]pMOT fragments examined. N-Terminal fragments of just over half the length of the native peptide are nearly equipotent as full-length motilin. These results suggest that the N-terminal segment, together with residues from the mid-portion of the molecule, constitutes the bioactive portion of pMOT. The C-terminal segment, in contrast, contributes little to receptor binding affinity or in vitro activity.

L19 ANSWER 325 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1992:358645 BIOSIS
DOCUMENT NUMBER: PREV199243036795; BR43:36795
TITLE: MOTILIN AND SMOOTH MUSCLE **MOTILIN RECEPTORS** IN THE CAT.
AUTHOR(S): DEPOORTERE I [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LAB, GASTHUISBERG O AND N, LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1992) Vol. 102, No. 4 PART 2, pp. A441.
Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 93RD ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION,

SAN FRANCISCO, CALIFORNIA, USA, MAY 9-15, 1992.
GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 30 Jul 1992
Last Updated on STN: 30 Jul 1992

L19 ANSWER 326 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1992:358592 BIOSIS
DOCUMENT NUMBER: PREV199243036742; BR43:36742
TITLE: CHRONIC ERYTHROMYCIN ADMINISTRATION INDUCES **MOTILIN RECEPTOR** DOWNREGULATION IN RABBIT COLONIC SMOOTH MUSCLE.
AUTHOR(S): BOLOGNA S [Reprint author]; HASLER W; OWYANG C
CORPORATE SOURCE: DEP INTERNAL MEDICINE, HENRY FORD HOSPITAL, DETROIT, MICH, USA
SOURCE: Gastroenterology, (1992) Vol. 102, No. 4 PART 2, pp. A428.
Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 93RD ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, SAN FRANCISCO, CALIFORNIA, USA, MAY 9-15, 1992.
GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 30 Jul 1992
Last Updated on STN: 30 Jul 1992

L19 ANSWER 327 OF 391 MEDLINE on STN DUPLICATE 150
ACCESSION NUMBER: 92234272 MEDLINE
DOCUMENT NUMBER: 92234272 PubMed ID: 1568663
TITLE: Erythromycin and the gut.
AUTHOR: Catnach S M; Fairclough P D
CORPORATE SOURCE: Department of Gastroenterology, St Bartholomew's Hospital, London.
SOURCE: GUT, (1992 Mar) 33 (3) 397-401. Ref: 43
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920612
Last Updated on STN: 19920612
Entered Medline: 19920528

AB The commonly reported gastrointestinal side effects that occur with erythromycin are related to its prokinetic action on the gut, mediated, at least in part, by its **motilin receptor** stimulating activity. This action may be of clinical use in conditions associated with gastrointestinal hypomotility such as diabetic gastroparesis and intestinal pseudo-obstruction, although further work needs to be done to establish the long term therapeutic uses of erythromycin in these disorders. Macrolide compounds with no antibacterial properties but which have a pronounced prokinetic action on the gut have already been synthesised and are currently being developed for future use in man. These 'motilides' should provide a useful addition to our rather limited armamentarium of effective gastrointestinal prokinetic agents.

L19 ANSWER 328 OF 391 MEDLINE on STN
ACCESSION NUMBER: 93255419 MEDLINE
DOCUMENT NUMBER: 93255419 PubMed ID: 1302371

TITLE: Erythromycin: a **motilin receptor** agonist.
AUTHOR: Shi X Z; Zhang J J
SOURCE: SHENG LI KO HSUEH CHIN CHAN [PROGRESS IN PHYSIOLOGICAL SCIENCES], (1992 Oct) 23 (4) 365-7. Ref: 26
Journal code: 20730140R. ISSN: 0559-7765.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19930618
Entered Medline: 19930608

L19 ANSWER 329 OF 391 MEDLINE on STN DUPLICATE 151
ACCESSION NUMBER: 92326803 MEDLINE
DOCUMENT NUMBER: 92326803 PubMed ID: 1385642
TITLE: Impairment of contractile response to carbachol and muscarinic receptor coupling in gastric antral smooth muscle cells isolated from diabetic streptozotocin-treated rats and db/db mice.
AUTHOR: Soulie M L; Cros G; Serrano J J; Bali J P
CORPORATE SOURCE: CNRS UPR-8402-INSERM U-249, Faculte de Pharmacie, Montpellier, France.
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (1992 Feb 12) 109 (2) 185-8.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920821
Last Updated on STN: 19980206
Entered Medline: 19920811

AB This work explored the role of the cholinergic pathway, assessed at a post-synaptic level by the use of isolated smooth muscle cells, in the impairment of antral motility associated with diabetic gastroparesis. Contractile response to carbachol--but not to erythromycin, a **motilin receptor** agonist--was abolished in antral smooth muscle cells isolated from (i) rats previously rendered diabetic by a single i.v. dose of streptozotocin (STZ, 60 mg/kg) and (ii) db/db spontaneously diabetic mice. Insulin treatment of STZ-rats was able to prevent the impairment of the carbachol contractile response, but not to reverse it once established. In STZ-rats, impairment of contractile response was not associated with a change in density of [3H]-N-methyl-scopolamine ([3H]-NMS) binding sites (approximately 1.5 fmol/mg protein). Displacement curve of the [3H]-NMS binding by carbachol was shifted to the right in diabetic rats as compared to controls. The addition of GTP-gamma-S induced a shift to the right of the displacement curve in control but not in diabetic animals. These results strongly suggest that diabetes is associated with an early and specific alteration of the muscarinic control of contraction of antral smooth muscles at a post-synaptic level, associated with an alteration of the GTP-binding proteins coupled to muscarinic receptors.

L19 ANSWER 330 OF 391 MEDLINE on STN DUPLICATE 152
ACCESSION NUMBER: 92157618 MEDLINE
DOCUMENT NUMBER: 92157618 PubMed ID: 1311048
TITLE: Erythromycin stimulates ileal motility by activation of dihydropyridine-sensitive calcium channels.
AUTHOR: Armstrong D N; Ballantyne G H; Modlin I M

CORPORATE SOURCE: Department of Surgery, Yale University School of Medicine, West Haven V.A. Medical Center, Connecticut 06510.
SOURCE: JOURNAL OF SURGICAL RESEARCH, (1992 Feb) 52 (2) 140-6. Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920410
Last Updated on STN: 19970203
Entered Medline: 19920326

AB Erythromycin, a macrolide antibiotic, is a potent stimulant of small bowel motor activity (MA) which may motility either via the peptide **motilin receptor** or neural mechanisms. We hypothesized that erythromycin stimulates directly stimulates smooth muscle cells by a calcium-mediated event. Thus, we evaluated the effect of neuronal blockade with tetrodotoxin, muscarinic blockade with atropine, and opiate blockade with naloxone on erythromycin-stimulated MA in isolated perfused segments of rabbit terminal ileum. We also tested the effect of nonspecific calcium channel blockade (verapamil and cadmiun) and specific blockade (dihydroxypyridine and nichol) on erythromycin-stimulated MA. MA was measured with a multichannel continuous perfusion manometry catheter. Erythromycin caused a concentration-dependent increase in MA (ED100 5 x 10(-4) M). Tetrodotoxin, atropine, and naloxone did not effect erythromycin-stimulated MA (P greater than 0.05). Both verapamil (10(-7) M) and cadmium (10(-2)-10(-4) M) inhibited erythromycin-stimulated MA. Selective blockade of "l" type calcium channels using dihydropyridine (10(-6) M) and "t" channels with nickel (10(-2)-10(-4) M) both reversed erythromycin-stimulated MA. Since the isolated segments of terminal ileum were free of exogenous humoral and neural effects, these studies indicated that erythromycin directly stimulated MA in the terminal ileum. Furthermore, since tetrodotoxin, atropine, and naloxone did not inhibit this increase in MA, erythromycin acted by a mechanism which was independent of the intrinsic nervous and opiate systems. In conclusion, these data are consistent with the model that erythromycin stimulates ileal motility by a mechanism involving activation of dihydroxypyridine and nickel-sensitive calcium channels.

L19 ANSWER 331 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 92:486965 SCISEARCH
THE GENUINE ARTICLE: JG987
TITLE: DISTRIBUTION AND CHARACTERIZATION OF **MOTILIN RECEPTORS** IN THE CAT
AUTHOR: DEPOORTERE I (Reprint); PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GASTHUISBERG O&N, GUT HORMONE LAB, LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: REGULATORY PEPTIDES, (23 JUL 1992) Vol. 40, No. 2, pp. 134 .
ISSN: 0167-0115.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 332 OF 391 MEDLINE on STN DUPLICATE 153
ACCESSION NUMBER: 92090670 MEDLINE
DOCUMENT NUMBER: 92090670 PubMed ID: 1727784
TITLE: Effect of motilin on gastric emptying in patients with diabetic gastroparesis.
AUTHOR: Peeters T L; Muls E; Janssens J; Urbain J L; Bex M; Van Cutsem E; Depoortere I; De Roo M; Vantrappen G; Bouillon R
CORPORATE SOURCE: Department of Medical Research, University of Leuven, Belgium.
SOURCE: GASTROENTEROLOGY, (1992 Jan) 102 (1) 97-101.

Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199201
ENTRY DATE: Entered STN: 19920216
Last Updated on STN: 19960129
Entered Medline: 19920130

AB Erythromycin markedly accelerates gastric emptying, possibly because it acts as a motilin agonist. In the present study, the effect of an equipotent dose of motilin was tested. In six patients with severe diabetic gastroparesis, gastric emptying of liquids and solids was examined scintigraphically after motilin or placebo in a double-blind crossover study. Motilin (10 pmol.kg-1.min-1) or saline was infused over a 90-minute period starting 5 minutes before breakfast. Motilin markedly accelerated emptying. For liquids, the half-emptying time was reduced from 51 +/- 6 to 22 +/- 11 minutes (P less than 0.01) and for solids from 111 +/- 4 to 51 +/- 12 minutes (P less than 0.01). The mean increase in plasma motilin levels was 1315 +/- 342 pg/mL, corresponding to an effective infusion rate of about 4 pmol.kg-1.min-1. In the control experiments, basal motilin levels (173 +/- 17 pg/mL) were within the normal range but increased steadily postprandially, reaching 321 +/- 25 pg/mL at the end of the study period, probably reflecting gastric distension. The postprandial increase in pancreatic polypeptide level was blunted compared with accepted normal values but was more pronounced during motilin infusion, i.e., 650 +/- 217 vs. 279 +/- 66 pg/mL (P less than 0.01), probably because of the improved emptying. Our data show that motilin accelerates gastric emptying in diabetic gastroparesis and support the hypothesis that erythromycin's effect is mediated through **motilin receptors.**

L19 ANSWER 333 OF 391 MEDLINE on STN DUPLICATE 154
ACCESSION NUMBER: 92168186 MEDLINE
DOCUMENT NUMBER: 92168186 PubMed ID: 1538793
TITLE: Motilin and erythromycin enhance the in vitro contractile activity of the sphincter of Oddi of the Australian brush-tailed possum.
AUTHOR: Baker R A; Saccone G T; Costi D; Thune A; Toouli J
CORPORATE SOURCE: Department of Surgery, Flinders University of South Australia, Bedford Park, Adelaide.
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1992 Jan) 345 (1) 71-7.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920417
Last Updated on STN: 19920417
Entered Medline: 19920402

AB Erythromycin has been shown to interact with gastrointestinal smooth muscle in a similar manner to motilin, and has been postulated as a **motilin receptor** agonist. We report that in isolated preparations from the biliary tract of thirty one Australian Brush-tailed Possums (Trichosurus vulpecula) erythromycin acts in a similar manner to motilin. In all muscle strips from the sphincter of Oddi, prepared in both the circular and longitudinal orientation, both synthetic porcine motilin (10(-10) M-10(-6) M) and erythromycin (lactobionate) (10(-8) M-10(-4) M) stimulated contractile activity in a concentration dependent manner, via a direct effect on the smooth muscle (the response was unaffected by tetrodotoxin, omega conotoxin GVIA or atropine). In strips

prepared from the gallbladder neither agonist affected the contractile activity in 7 of 8 animals. Motilin was approximately 1000 fold more potent in stimulating contractile activity than erythromycin in both sphincter of Oddi circular strips [pD2 for peak response to motilin 8.67 (mean) +/- 0.06 (SEM) compared with erythromycin 5.67 +/- 0.09] and sphincter of Oddi longitudinal strips [pD2 for peak response to motilin 8.64 (mean) +/- 0.28 (SEM) compared with erythromycin 5.45 +/- 0.23]. The concentration response curves for motilin and erythromycin were similar and both agonists required the presence of extracellular calcium to elicit responses (responses were diminished by verapamil and abolished in calcium free Krebs solution). Our results support the hypothesis that erythromycin mimics the action of motilin in stimulating the sphincter of Oddi in vitro.

L19 ANSWER 334 OF 391 MEDLINE on STN DUPLICATE 155
ACCESSION NUMBER: 92125475 MEDLINE
DOCUMENT NUMBER: 92125475 PubMed ID: 1733270
TITLE: Erythromycin contracts rabbit colon myocytes via occupation of **motilin receptors.**
AUTHOR: Hasler W L; Heldsinger A; Chung O Y
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109.
CONTRACT NUMBER: P30 DK-34933 (NIDDK)
RO1 DK-35783 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1992 Jan) 262 (1 Pt 1) G50-5.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920315
Last Updated on STN: 19920315
Entered Medline: 19920221

AB Erythromycin stimulates gastroduodenal motility via action on **motilin receptors.** We evaluated erythromycin as a colonic muscle motilin agonist using in vitro rabbit colon studies. Isolated myocytes contracted to erythromycin with a half-maximal effective concentration of 2 pM and peak shortening of 22.4 +/- 2.5% at 1 nM, which was superimposable with the response to motilin. 125I-labeled motilin binding to colon muscle homogenates was saturable and specific with a dissociation constant (Kd) of 0.39 nM and maximal binding (Bmax) of 41 +/- 3 fmol/mg protein. Motilin displaced specifically bound 125I-motilin, with a Kd of 0.31 nM. Erythromycin displaced 125I-motilin but was less potent, with an inhibitory constant of 84.0 nM. Bmax values from displacement studies were similar to the Scatchard data. **Motilin receptor** protection from alkylation by N-ethylmaleimide preserved contraction to motilin and erythromycin but not acetylcholine or cholecystokinin, whereas protection with erythromycin preserved contraction to motilin but not other agonists. In conclusion, erythromycin binds to colon muscle **motilin receptors** present in densities similar to reported values for the upper gut. Furthermore, erythromycin contracts colonic myocytes via specific action on **motilin receptors.** Thus erythromycin may have colonic motor-stimulating properties by action on **motilin receptors.**

L19 ANSWER 335 OF 391 MEDLINE on STN
ACCESSION NUMBER: 91215611 MEDLINE
DOCUMENT NUMBER: 91215611 PubMed ID: 2021948
TITLE: The relationship between motility factor receptor internalization and the lung colonization capacity of murine melanoma cells.
AUTHOR: Watanabe H; Nabi I R; Raz A

CORPORATE SOURCE: Cancer Metastasis Program, Michigan Cancer Foundation, Detroit, Michigan 48201.
SOURCE: CANCER RESEARCH, (1991 May 15) 51 (10) 2699-705. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199106
ENTRY DATE: Entered STN: 19910623
Last Updated on STN: 20021218
Entered Medline: 19910603

AB The in vitro motility of B16-F1 melanoma cells is enhanced by incubation with a monoclonal antibody against gp78, previously characterized as a motility factor receptor. This antibody was used to study the relationship between motility stimulation in vitro and metastatic ability in vivo in the B16-F1 and K-1735 murine melanoma systems. While both high- and low-metastatic variants exhibited enhanced in vitro motility in response to the anti-gp78 monoclonal antibody, only the high-metastatic cells exhibited an increased metastatic ability. Surface immunofluorescence of low-metastatic cells was distributed more diffusely compared to a highly localized patching of gp78 on high-metastatic cells, suggesting that the directed endocytosis of gp78 to form a single leading edge is related to the metastatic ability of a cell, while fluorescence-activated cell sorter analysis revealed decreased gp78 surface expression in high-metastatic clones. Priming of cells by preventing internalization of gp78-antibody complexes by pertussis toxin resulted in a marked enhancement of pulmonary metastases by the treated cells which was directly correlated with decreased surface expression of gp78 following washout of pertussis toxin. These results suggest that cell motility induced by motility factor receptor occupancy may play a role in the process of metastasis and that the ligand-receptor complex internalization from the cell surface is involved in control of cell kinesis during metastasis.

L19 ANSWER 336 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1992:108448 BIOSIS
DOCUMENT NUMBER: PREV199242048448; BR42:48448
TITLE: ORAL AND INTRAVENOUS ERYTHROMYCIN HAS NO EFFECT ON DISTAL HUMAN COLONIC MOTILITY.
AUTHOR(S): JAMESON J S [Reprint author]; ROGERS J; RAIMUNDO A H; HENRY M M; MISIEWICZ J J
CORPORATE SOURCE: DEP GASTROENTEROLOGY NUTRITION, CENTRAL MIDDLESEX HOSPITAL, LONDON, UK
SOURCE: Gut, (1991) Vol. 32, No. 10, pp. A1216. Meeting Info.: AUTUMN MEETING OF THE BRITISH SOCIETY OF GASTROENTEROLOGY, COVENTRY, ENGLAND, UK, SEPTEMBER 9-11, 1991. GUT. CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 24 Feb 1992
Last Updated on STN: 24 Feb 1992

L19 ANSWER 337 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:380353 BIOSIS
DOCUMENT NUMBER: PREV199141052743; BR41:52743
TITLE: ACTIVATION OF ANTRAL AND COLONIC **MOTILIN RECEPTORS.**
AUTHOR(S): BRADETTE M [Reprint author]; RIBERDY M; RAYMOND M C; POITRAS P; BOIVIN M
CORPORATE SOURCE: ANDRE-VIALLET CLIN RES CENT, ST-LUC HOSP, MONTREAL, CAN
SOURCE: Gastroenterology, (1991) Vol. 100, No. 5 PART 2, pp. A632. Meeting Info.: DIGESTIVE DISEASE WEEK AND THE 92ND ANNUAL

MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, NEW ORLEANS, LOUISIANA, USA, MAY 19-22, 1991.
GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 17 Aug 1991
Last Updated on STN: 8 Oct 1991

L19 ANSWER 338 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:464800 BIOSIS
DOCUMENT NUMBER: PREV199141090560; BR41:90560
TITLE: ERYTHROMYCIN AS A PROKINETIC AGENT.
AUTHOR(S): TURNER C L [Reprint author]; CROTEAU D
CORPORATE SOURCE: GEN HOSP, GEY NUNS EDMONTON, EDMONTON, ALBERTA
SOURCE: Canadian Journal of Hospital Pharmacy, (1991) Vol. 44, No. 4, pp. 211.
CODEN: CJHPAV. ISSN: 0008-4123.
DOCUMENT TYPE: Article
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 21 Oct 1991
Last Updated on STN: 21 Oct 1991

L19 ANSWER 339 OF 391 MEDLINE on STN DUPLICATE 156
ACCESSION NUMBER: 91296054 MEDLINE
DOCUMENT NUMBER: 91296054 PubMed ID: 2067593
TITLE: Ca2+ dependence of motilide-induced contractions in rabbit duodenal muscle strips in vitro.
AUTHOR: Peeters T L; Matthijs G; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Kaholieke Universiteit te Leuven, Gasthuisberg, Belgium.
SOURCE: NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1991 Feb) 343 (2) 202-8.
Journal code: 0326264. ISSN: 0028-1298.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910901
Last Updated on STN: 19910901
Entered Medline: 19910814

AB Recent studies suggested that certain erythromycin A (EM-A) derivatives are **motilin receptor** agonists. As proposed by Itoh they may be called "motilides". We have investigated the Ca2(+)-dependence of contractions induced by two potent motilides, ME-34 [de(N-methyl) 8,9-anhydroeryhtromycin A 6,9-hemiacetal] and EM-523 [de(N-methyl)-N-ethyl-8,9-anhydroerythromycin A 6,9-hemiacetal], in duodenal tissues and compared the results with those previously obtained with motilin. Isometric and isotonic contractile responses of isolated longitudinal muscle sheets from the rabbit duodenum were tested under normal, Ca2(+)-free and depolarizing conditions. Prior to stimulation with motilides, the maximal response to acetylcholine was recorded and all responses were always expressed as a percentage of this response. Both motilides induced contractions in normally polarized tissue, with an EC50 of 26 +/- 5 nM for ME-34 (n = 7), and 27 +/- 5 nM for EM-523 (n = 16) and maximal responses of respectively 88 +/- 4% and 80 +/- 3%. Like motilin, both compounds induced an 'extra'-contraction in depolarized tissues. The EM-523 response in 140 mM K+ under isotonic conditions was 84 +/- 3% (n = 5) at 10(-5) M, with an EC50 that was shifted to 65 +/- 18 nM. Similar figures were obtained for ME-34. When Ca2+ was added to Ca2(+)-depleted strips, half-maximal Ca2+ values (in mM) were 1.10 +/- 0.11 (n = 9) for EM-523 and 1.13 +/- 0.12 (n = 3) for ME-34, as compared with 1.12 +/- 0.13

(n = 7) for motilin and 2.8 +/- 1.1 (n = 9) for K+. Both ME-34 and EM-523 also induced a transient contraction in Ca2(+)-free solutions under isometric conditions.(ABSTRACT TRUNCATED AT 250 WORDS)

L19 ANSWER 340 OF 391 MEDLINE on STN DUPLICATE 157
ACCESSION NUMBER: 91271091 MEDLINE
DOCUMENT NUMBER: 91271091 PubMed ID: 2052502
TITLE: **Motilin receptors** of the rabbit colon.
AUTHOR: Depoortere I; Peeters T L; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: PEPTIDES, (1991 Jan-Feb) 12 (1) 89-94.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910811
Last Updated on STN: 19910811
Entered Medline: 19910722

AB Binding studies with iodinated motilin revealed that in the small intestine **motilin receptor** density decreased aborally, disappeared in the caecum but returned in the colon and rectum. The highest density was in the distal colon (112 +/-/11 fmol/mg protein). The dissociation constant was the same in all regions (overall mean 1.10 +/- 0.22 nM). The ability of erythromycin-A (EM-A) and of two derivatives, EM-A N-oxide and EM-523, to displace motilin showed no difference between the tissues studied. Their order of potency was: motilin greater than EM-523 greater than EM-A greater than EM-A N-oxide. Proximal circular colonic smooth muscle strips showed maximal contractile responses towards motilin, EM-523 and EM-A of, respectively, 80 +/- 3%, 78 +/- 4% and 84 +/- 2% relative to the maximum obtained with acetylcholine. In proximal longitudinal muscle only a response of +/- 20% was obtained. Similar responses were obtained in the distal colon. The order of potency to induce contractions as reflected in the pED50 values was: motilin (8.03 +/- 0.1) greater than EM-523 (7.55 +/- 0.03) greater than EM-A (5.84 +/- 0.04) in proximal circular colon. The responses were not blocked by TTX (10(-6) M) or atropine (10(-6) M), but were reduced by verapamil (10(-6)M). The abundance of **motilin receptors** in colonic smooth muscle, if applicable to other species, opens new perspectives for the therapeutic applications of macrolides with motilin agonist properties.

L19 ANSWER 341 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:117106 SCISEARCH
THE GENUINE ARTICLE: EY791
TITLE: **MOTILIN RECEPTORS** OF THE RABBIT COLON
AUTHOR: DEPOORTERE I; PEETERS T L (Reprint); VANTRAPPEN G
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, CTR GASTROENTEROL RES, DEPT MED RES, GUT HORMONE LAB, GASTHUISBERG ON, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: PEPTIDES, (1991) Vol. 12, No. 1, pp. 89-94.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 23
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Binding studies with iodinated motilin revealed that in the small intestine **motilin receptor** density decreased aborally, disappeared in the caecum but returned in the colon and rectum. The highest density was in the distal colon (112 +/- /11 fmol/mg protein). The dissociation constant was the same in all regions (overall mean 1.10 +/- 0.22 nM). The ability of erythromycin-A (EM-A) and of two derivatives, EM-A N-oxide and EM-523, to displace motilin showed no

difference between the tissues studied. Their order of potency was: motilin > EM-523 > EM-A > EM-A N-oxide. Proximal circular colonic smooth muscle strips showed maximal contractile responses towards motilin, EM-523 and EM-A of, respectively, 80 +/- 3%, 78 +/- 4% and 84 +/- 2% relative to the maximum obtained with acetylcholine. In proximal longitudinal muscle only a response of +/- 20% was obtained. Similar responses were obtained in the distal colon. The order of potency to induce contractions as reflected in the pED50 values was: motilin (8.03 +/- 0.1) > EM-523 (7.55 +/- 0.03) > EM-A (5.84 +/- 0.04) in proximal circular colon. The responses were not blocked by TTX (10(-6) M) or atropine (10(-6) M), but were reduced by verapamil (10(-6) M). The abundancy of **motilin receptors** in colonic smooth muscle, if applicable to other species, opens new perspectives for the therapeutic applications of macrolides with motilin agonist properties.

L19 ANSWER 342 OF 391 MEDLINE on STN DUPLICATE 158
ACCESSION NUMBER: 91239842 MEDLINE
DOCUMENT NUMBER: 91239842 PubMed ID: 2034624
TITLE: Effect of erythromycin and of octreotide on **motilin receptor** density in the rabbit.
AUTHOR: Depoortere I; Peeters T L; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: REGULATORY PEPTIDES, (1991 Feb 1) 32 (2) 85-94.
Journal code: 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199106
ENTRY DATE: Entered STN: 19910714
Last Updated on STN: 19910714
Entered Medline: 19910625

AB Recent studies have shown that erythromycin lactobionate (EMLB) acts as a motilin agonist and is able to accelerate gastric emptying in diabetic gastroparesis. Using the rabbit as a model, we have studied the changes in **motilin receptor** density induced by EMLB (a motilin agonist) and octreotide (a somatostatin analogue and an inhibitor of motilin secretion). Binding studies were performed with antral smooth muscle tissue homogenates using iodinated nor-leucine13-porcine-motilin, and binding parameters were obtained from computerized fits to displacement curves. The contractile capacity towards motilin (10(-7) M) and EMLB (10(-5) M) was measured isotonically on duodenal segments and the response was expressed relative to the maximum obtained with ACh (10(-4) M). The first hours after the last i.v. administrations of EMLB (50 mg/day given on 3 consecutive days), motilin binding was completely abolished to 0.02 +/- 0.006 fmol/mg protein, compared to the control group (0.64 +/- 0.12 fmol/mg protein). The effect was dose-related: total doses of 17.5 mg, 87.5 mg, 175 mg EMLB reduced motilin binding and contractility towards motilin and EMLB to respectively 95 +/- 10, 82 +/- 5%; 36 +/- 9, 38 +/- 9%; 3 +/- 1, 24 +/- 2% of the control values. The effect was also long lasting: binding was still reduced to 60% of the control value 48 h after the highest dose. In contrast, octreotide induced a marked but short lasting upregulation. After 3 daily s.c. injections of 5 micrograms, Bmax rose to 13.6 +/- 1.9 fmol/mg protein (P less than 0.05). It was already obtained 1 h after 3 x 2.5 micrograms/24 h. The changes in receptor-density were not related to changes in affinity. We conclude that **motilin receptors** can be regulated by EMLB and octreotide presumably because one compound mimicks hypermotilinemia, the other one induces hypomotilinemia.

L19 ANSWER 343 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:103687 SCISEARCH
THE GENUINE ARTICLE: EY260
TITLE: EFFECT OF ERYTHROMYCIN AND OF OCTREOTIDE ON

MOTILIN RECEPTOR DENSITY IN THE RABBIT
AUTHOR: DEPOORTERE I; PEETERS T L (Reprint); VANTRAPPEN G
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, GASTHUISBERG ON, DEPT MED RES, CTR GASTROENTEROL RES, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: REGULATORY PEPTIDES, (1991) Vol. 32, No. 2, pp. 85-94.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 27

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Recent studies have shown that erythromycin lactobionate (EMLB) acts as a motilin agonist and is able to accelerate gastric emptying in diabetic gastroparesis. Using the rabbit as a model, we have studied the changes in **motilin receptor** density induced by EMLB (a motilin agonist) and octreotide (a somatostatin analogue and an inhibitor of motilin secretion). Binding studies were performed with antral smooth muscle tissue homogenates using iodinated nor-leucine13-porcine-motilin, and binding parameters were obtained from computerized fits to displacement curves. The contractile capacity towards motilin (10(-7) M) and EMLB (10(-5) M) was measured isotonically on duodenal segments and the response was expressed relative to the maximum obtained with ACh (10(-4) M). The first hours after the last i.v. administrations of EMLB (50-mg/day given on 3 consecutive days), motilin binding was completely abolished to 0.02 +/- 0.006 fmol/mg protein, compared to the control group (0.64 +/- 0.12 fmol/mg protein). The effect was dose-related: total doses of 17.5 mg, 87.5 mg, 175 mg EMLB reduced motilin binding and contractility towards motilin and EMLB to respectively 95 +/- 10, 82 +/- 5%; 36 +/- 9, 38 +/- 9%; 3 +/- 1, 24 +/- 2% of the control values. The effect was also long lasting: binding was still reduced to 60% of the control value 48 h after the highest dose. In contrast, octreotide induced a marked but short lasting upregulation. After 3 daily s.c. injections of 5-mu-g, B(max) rose to 13.6 +/- 1.9 fmol/mg protein ($P < 0.05$). It was already obtained 1 h after 3 x 2.5-mu-g/24 h. The changes in receptor-density were not related to changes in affinity. We conclude that **motilin receptors** can be regulated by EMLB and octreotide presumably because one compound mimicks hypermotilinemia, the other one induces hypomotilinemia.

L19 ANSWER 344 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1992:19675 BIOSIS
DOCUMENT NUMBER: PREV199242007375; BR42:7375
TITLE: ACTIVATION OF ANTRAL AND COLONIC **MOTILIN RECEPTORS.**
AUTHOR(S): BRADETTE M [Reprint author]; RIBERDY M; RAYMOND M C; POITRAS P; BOIVIN M
CORPORATE SOURCE: ANDRE-VIALLET CLIN RES CENTER, ST-LUC HOSP, MONTREAL, CANADA
SOURCE: Clinical and Investigative Medicine, (1991) Vol. 14, No. 4 SUPPL, pp. A45.
Meeting Info.: ABSTRACTS FROM THE ANNUAL MEETING OF THE CANADIAN SOCIETY FOR CLINICAL INVESTIGATION, THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA AND PARTICIPATING SOCIETIES, QUEBEC, CANADA, SEPTEMBER 19-23, 1991. CLIN INVEST MED.
CODEN: CNVMDL. ISSN: 0147-958X.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 18 Dec 1991
Last Updated on STN: 6 Mar 1992

L19 ANSWER 345 OF 391 MEDLINE on STN
ACCESSION NUMBER: 91289666 MEDLINE

DOCUMENT NUMBER: 91289666 PubMed ID: 1648290
TITLE: [Medicamentous modification of gastrointestinal motility and secretion].
Medikamentose Beeinflussung der gastro-intestinalen Motilitat und Sekretion.
AUTHOR: Allescher H D
CORPORATE SOURCE: II. Medizinische Klinik und Poliklinik TU Munchen.
SOURCE: ZEITSCHRIFT FUR GASTROENTEROLOGIE, (1991 Apr) 29 Suppl 3 27-30. Ref: 34
Journal code: 0033370. ISSN: 0044-2771.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910825
Last Updated on STN: 19910825
Entered Medline: 19910805

AB This article gives an overview on possible new pharmacological tools to modify gastrointestinal motility and/or secretion. The characterization of new subclasses of classical neurotransmitter receptors and of peptidergic receptors offer a new approach for the development of new therapeutic agents. Using molecular biology techniques a variety of receptor subclasses have been demonstrated for muscarinic and alpha 2-adrenergic receptors. Both receptor types are of major importance for the regulation of mucosal secretion in the submucosal plexus and specific ligands for these receptor subtypes could be of clinical interest. In the next paragraphs the possible therapeutic relevance of 5-HT3-receptor antagonists and of opiate agonist and -antagonists is discussed. 5-HT3-antagonists, which can be used as potent antiemetics, also demonstrate quite potent effects on upper gastrointestinal motility such as gastric emptying. Whereas the subclassification of opioids has so far no specific therapeutic consequences there is some evidence that casomorphin, a derivative of the casein of the milk, could be used as a possible antidiarhoic substance. The use of antagonist and agonists on peptidergic receptors with orally active ligands offer a further new therapeutic approach. This is discussed for CCK-antagonists and erythromycin-analogues which are agonists at the **motilin receptor.** Besides this experimental approach to modify defined receptor subclasses, there are new substances with so far not clearly defined mechanism of action, which, however, have potent therapeutic effects. Cisapride, a new potent prokinetic drug with little side effects, is now available for clinical use for a wide range of motility disorders.

L19 ANSWER 346 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:306524 SCISEARCH
THE GENUINE ARTICLE: FM806
TITLE: PHARMACOLOGICAL MODULATION OF GASTROINTESTINAL MOTILITY AND SECRETION
AUTHOR: ALLESCHER H D (Reprint)
CORPORATE SOURCE: TECH UNIV MUNICH, MED KLIN & POLIKLIN 2, ISMANINGER STR 22, W-8000 MUNICH 80, GERMANY (Reprint)
COUNTRY OF AUTHOR: GERMANY
SOURCE: ZEITSCHRIFT FUR GASTROENTEROLOGIE, (1991) Vol. 29, pp. 27-30.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: German
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This article gives an overview on possible new pharmacological tools to modify gastrointestinal motility and/or secretion. The characterization

of new subclasses of classical neurotransmitter receptors and of peptidergic receptors offer a new approach for the development of new therapeutic agents. Using molecular biology techniques a variety of receptor subclasses have been demonstrated for muscarinic and alpha 2-adrenergic receptors. Both receptor types are of major importance for the regulation of mucosal secretion in the submucosal plexus and specific ligands for these receptor subtypes could be of clinical interest. In the next paragraphs the possible therapeutic relevance of 5-HT3-receptor antagonists and of opiate agonist and -antagonists is discussed. 5-HT3-antagonists, which can be used as potent antiemetics, also demonstrate quite potent effects on upper gastrointestinal motility such as gastric emptying. Whereas the subclassification of opioids has so far no specific therapeutic consequences there is some evidence that casomorphin, a derivative of the casein of the milk, could be used as a possible antidiarhoic substance. The use of antagonist and agonists on peptidergic receptors with orally active ligands offer a further new therapeutic approach. This is discussed for CCK-antagonists and erythromycin-analogues which are agonists at the **motilin receptor.** Besides this experimental approach to modify defined receptor subclasses, there are new substances with so far not clearly defined mechanism of action, which, however, have potent therapeutic effects. Cisapride, a new potent prokinetic drug with little side effects, is now available for clinical use for a wide range of motility disorders.

L19 ANSWER 347 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1990:249954 BIOSIS
DOCUMENT NUMBER: PREV199038116542; BR38:116542
TITLE: **MOTILIN RECEPTORS.**
AUTHOR(S): PEETERS T L [Reprint author]; VANTRAPPEN G; DEPOORTERE I
CORPORATE SOURCE: CENTER GASTROENTEROLOGICAL RES, UNIV LEUVEN, B-3000 LEUVEN, BELGIUM
SOURCE: (1990) pp. 93-110. ITOH, Z. (ED.). MOTILIN. XVII+264P. ACADEMIC PRESS, INC.: SAN DIEGO, CALIFORNIA, USA; LONDON, ENGLAND, UK. ILLUS.
ISBN: 0-12-375730-4.
DOCUMENT TYPE: Book
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 23 May 1990
Last Updated on STN: 31 May 1990

L19 ANSWER 348 OF 391 MEDLINE on STN DUPLICATE 159
ACCESSION NUMBER: 90205981 MEDLINE
DOCUMENT NUMBER: 90205981 PubMed ID: 2320062
TITLE: Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies.
COMMENT: Comment in: N Engl J Med. 1990 Apr 12;322(15):1078-9
AUTHOR: Janssens J; Peeters T L; Vantrappen G; Tack J; Urbain J L; De Roo M; Muls E; Bouillon R
CORPORATE SOURCE: Department of Internal Medicine, University Hospital Gasthuisberg, University of Leuven, Belgium.
SOURCE: NEW ENGLAND JOURNAL OF MEDICINE, (1990 Apr 12) 322 (15) 1028-31.
Journal code: 0255562. ISSN: 0028-4793.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199004
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19970203

Entered Medline: 19900427

AB Erythromycin mimics the effect of the gastrointestinal polypeptide motilin on gastrointestinal motility, probably by binding to **motilin receptors** and acting as a motilin agonist. Erythromycin may thus have clinical application in patients with disturbances of gastroduodenal motility, such as diabetic gastroparesis. To examine this possibility, we studied the effect of erythromycin on gastric emptying in 10 patients with insulin-dependent diabetes mellitus and gastroparesis. We studied the emptying of liquids and solids simultaneously on separate days after the intravenous administration of erythromycin (200 mg) or placebo, using a double-isotope technique and a double-blind, crossover design. Erythromycin shortened the prolonged gastric-emptying times for both liquids and solids to normal. For example, 120 minutes after the ingestion of a solid meal, mean (+/- SE) retention was 63 +/- 9 percent with placebo and 4 +/- 1 percent with erythromycin, as compared with 9 +/- 3 percent in 10 healthy subjects. The corresponding values 120 minutes after the ingestion of a liquid meal were 32 +/- 4, 9 +/- 3, and 4 +/- 1 percent, respectively. Gastric emptying also improved, but to a lesser degree, in the 10 patients after four weeks of treatment with oral erythromycin (250 mg three times a day). These preliminary results suggest that erythromycin may have therapeutic value in patients with severe diabetic gastroparesis.

L19 ANSWER 349 OF 391 MEDLINE on STN
ACCESSION NUMBER: 90331279 MEDLINE
DOCUMENT NUMBER: 90331279 PubMed ID: 2376894
TITLE: Motilin--structure and tissue specific expression of the human motilin gene and **motilin receptor** .
AUTHOR: Yano H; Seino Y
CORPORATE SOURCE: Department of Medicine, Kyoto University School of Medicine.
SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1990 May) 48 (5) 1005-10.
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901012
Last Updated on STN: 19901012
Entered Medline: 19900905

L19 ANSWER 350 OF 391 MEDLINE on STN DUPLICATE 160
ACCESSION NUMBER: 90337138 MEDLINE
DOCUMENT NUMBER: 90337138 PubMed ID: 2379773
TITLE: Development of **motilin receptors** and of motilin- and erythromycin-induced contractility in rabbits.
AUTHOR: Depoortere I; Peeters T L; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: GASTROENTEROLOGY, (1990 Sep) 99 (3) 652-8.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901012
Last Updated on STN: 20020212
Entered Medline: 19900913

AB The development of the **motilin receptor** was studied through contraction and binding studies of groups of three rabbits aged between 2 and 289 days. The contractility of small intestinal smooth

muscle strips was measured isotonically. The aborally decreasing gradient in response to motilin, known to exist in adult rabbits, was already present at day 8 (maximum contractile responses expressed as a percent of the maximal response to acetylcholine were 77% +/- 9%, 34% +/- 10%, and 25% +/- 8% for duodenal, jejunal, and ileal strips, respectively). Throughout the observation period, the doses of motilin and its agonist erythromycin that were required to induce 50% of the response remained constant and were not significantly different from doses required for adults (their negative logarithms were 8.55 +/- 0.35 and 5.70 +/- 0.25, respectively). The correlation between the maximum contractile response toward motilin and erythromycin was almost perfect (r2 = 0.82). Binding studies with iodinated norleucine13-porcine motilin were performed using antral smooth muscle tissue homogenates. The maximum number of binding sites increased rapidly after 8 days (3.3 +/- 0.4 fmol/mg protein) and reached a peak at 21 days (20.7 +/- 1.4 fmol/mg protein), but decreased at that point toward the adult value (40 days, 10.6 +/- 1.3; 289 days, 9.8 +/- 1.1 fmol/mg protein). The dissociation constant, however, remained unchanged. The peak value of receptor density occurred at about the time that the rate of increase of the length of the intestine and of the weight of the antrum were at maximum levels (at 18 and 27 days, respectively). **Motilin receptors** are expressed early postnatally, and the regional gradient in sensitivity towards motilin is also established soon after birth. If applicable to humans, an early response to erythromycin may have therapeutic value.

L19 ANSWER 351 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 90:438475 SCISEARCH
THE GENUINE ARTICLE: DU077
TITLE: DEVELOPMENT OF **MOTILIN RECEPTORS** AND OF MOTILIN-INDUCED AND ERYTHROMYCIN-INDUCED CONTRACTILITY IN RABBITS
AUTHOR: DEPOORTERE I; PEETERS T L (Reprint); VANTRAPPEN G
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, DEPT MED RES, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GASTROENTEROLOGY, (1990) Vol. 99, No. 3, pp. 652-658.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 24

L19 ANSWER 352 OF 391 MEDLINE on STN
ACCESSION NUMBER: 90358717 MEDLINE
DOCUMENT NUMBER: 90358717 PubMed ID: 2202281
TITLE: Gastrointestinal hormones: from basic science to a clinical perspective.
AUTHOR: Shulkes A
CORPORATE SOURCE: Department of Surgery, University of Melbourne, Austin Hospital, Victoria, Australia.
SOURCE: AUSTRALIAN AND NEW ZEALAND JOURNAL OF SURGERY, (1990 Aug) 60 (8) 575-8. Ref: 31
Journal code: 0373115. ISSN: 0004-8682.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901026
Last Updated on STN: 19901026
Entered Medline: 19900921

AB The gastrointestinal tract is the largest endocrine organ in the body. However, gastrointestinal hormones are not confined to the gut and many of them are delivered to their target tissue by neural and paracrine routes

as well as the circulation. Regulatory peptide is therefore a more appropriate term than gastrointestinal hormone. The functions of these regulatory peptides include effects on intake, digestion and absorption of food, and changes in gut secretions, motility and growth. Since these peptides do not act alone but in concert it has been difficult to ascribe particular functions to individual peptides. However, the recent and on-going development of specific regulatory peptide agonists and antagonists has resulted in major advances in our understanding of the physiology of these peptides. In turn these findings are creating new therapeutic avenues providing some return from all the research on these gastrointestinal regulatory peptides. The somatostatin derivative (octreotide or sandostatin) is the most obvious example. Although only approved in Australia for treatment of carcinoids and VIPomas, the prospects include treatment of other gastroenteropancreatic tumours, acromegaly, idiopathic diarrhoea, fistula closure, dumping, and ERCP or post-operative pancreatitis. A new gastrokinetic agent, that acts via the **motilin receptor**, is undergoing trials for the treatment of impaired gastric emptying. The trophic effect of gastrointestinal peptides has clinical significance. For instance, gastrin antagonists inhibit cell proliferation of colon carcinoma cell lines. Furthermore the trophic effect of gastrin must be considered when potent gastric acid inhibitors, which cause a reflex increase in gastrin, are used. The outlook is for more mammalian regulatory peptides to be discovered adding further to the complexity.(ABSTRACT TRUNCATED AT 250 WORDS)

L19 ANSWER 353 OF 391 MEDLINE on STN DUPLICATE 161
ACCESSION NUMBER: 92024782 MEDLINE
DOCUMENT NUMBER: 92024782 PubMed ID: 2130582
TITLE: [Pseudo-obstruction of the stomach and small intestines]. La pathologie pseudo-obstructive du grele et de l'estomac.
AUTHOR: Vantrappen G; Janssens J
CORPORATE SOURCE: Service de Medecine Interne et Gastro-enterologie, Hopital Universitaire Gasthuisberg, Leuven.
SOURCE: ACTA GASTROENTEROLOGICA BELGICA, (1990 Sep-Dec) 53 (5-6) 523-31. Ref: 10
Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199111
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19920124
Entered Medline: 19911121

AB The authors review the pathological classification of chronic pseudo-obstruction syndromes, the differential diagnosis of these syndromes in order to rule out an obstructive lesion, the differential diagnosis of idiopathic chronic pseudo-obstruction syndrome and systemic sclerosis, the diagnostic contribution of oesophageal manometry and of gastro-intestinal manometry and electromyography, and finally the treatment of these syndromes. The authors mention also their experience in the treatment of severe diabetic gastroparesis with erythromycin, agonist of the gastric and duodenal **motilin receptors.** In 10 patients compared to controls, delayed gastric emptying for solid and liquid foods was normalized after intravenous injection of 200 mg erythromycin versus placebo.

L19 ANSWER 354 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 91:561957 SCISEARCH
THE GENUINE ARTICLE: GJ312
TITLE: PSEUDOOBSTRUCTION OF THE STOMACH AND SMALL-INTESTINE
AUTHOR: VANTRAPPEN G (Reprint); JANSSENS J
CORPORATE SOURCE: HOP UNIV GASTHUISBERG, SERV MED INTERNE & GASTROENTEROL,

HERESTR 49, B-3000 LOUVAIN, BELGIUM (Reprint)
COUNTRY OF AUTHOR: BELGIUM
SOURCE: ACTA GASTRO-ENTEROLOGICA BELGICA, (1990) Vol. 53, No. 5-6, pp. 523-531.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: French
REFERENCE COUNT: No References Keyed
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The authors review the pathological classification of chronic pseudo-obstruction syndromes, the differential diagnosis of these syndromes in order to rule out an obstructive lesion, the differential diagnosis of idiopathic chronic pseudo-obstruction syndrome and systemic sclerosis, the diagnostic contribution of oesophageal manometry and of gastro-intestinal manometry and electromyography, and finally the treatment of these syndromes. The authors mention also their experience in the treatment of severe diabetic gastroparesia with erythromycin, agonist of the gastric and duodenal **motilin receptors.** In 10 patients compared to controls, delayed gastric emptying for solid and liquid foods was normalized after intravenous injection of 200 mg erythromycin versus placebo.

L19 ANSWER 355 OF 391 MEDLINE on STN DUPLICATE 162
ACCESSION NUMBER: 90341091 MEDLINE
DOCUMENT NUMBER: 90341091 PubMed ID: 2381873
TITLE: The erythromycin derivative EM-523 is a potent motilin agonist in man and in rabbit.
AUTHOR: Depoortere I; Peeters T L; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: PEPTIDES, (1990 May-Jun) 11 (3) 515-9.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901012
Last Updated on STN: 19901012
Entered Medline: 19900913

AB Erythromycin may stimulate gastrointestinal motor activity via its effect upon **motilin receptors.** We have studied the ability of the derivative EM-523 [de(N-methyl)-N-ethyl-8,9-anhydroerythromycin A 6,9-hemiacetal] to induce contractions in duodenal smooth muscle strips and to displace labeled motilin bound to antral smooth muscle, in man and in rabbit. In both species EM-523 approached the potency of motilin for inducing contractions. Thus pED50 values were 7.84 +/- 0.11 and 8.69 +/- 0.12 for motilin in, respectively, man and rabbit, against 6.08 +/- 0.13 and 8.19 +/- 0.10 for EM-523. In rabbit the efficacy of both compounds decreased in parallel aborally, the responses to EM-523 could not be blocked by atropine (10(-7) M) or TTX (10(-7) M), and both compounds were unable to further enhance the maximum effect to the other compound. In binding studies the order of potency was the same as in the contraction studies. The pIC50 values were: motilin (8.84 +/- 0.31, 9.17 +/- 0.20) greater than EM-523 (7.89 +/- 0.1, 8.40 +/- 0.10). A Schild plot revealed that EM-523 was a competitive inhibitor of **motilin receptor** binding in man and in rabbit. We conclude that EM-523 is a potent motilin agonist.

L19 ANSWER 356 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1990:299567 BIOSIS
DOCUMENT NUMBER: PREV199039017748; BR39:17748
TITLE: THE **MOTILIN RECEPTOR** IS COUPLED TO A G-PROTEIN.
AUTHOR(S): DEPOORTERE I [Reprint author]; PEETERS T L; VANTRAPPEN G

CORPORATE SOURCE: GUT HORMONE LAB, GASTHUISBERG O AND N, LEUVEN, BELG
SOURCE: Gastroenterology, (1990) Vol. 98, No. 5 PART 2, pp. A489. Meeting Info.: 91ST ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION AND DIGESTIVE DISEASE WEEK, SAN ANTONIO, TEXAS, USA, MAY 12-18, 1990. GASTROENTEROLOGY. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Jun 1990
Last Updated on STN: 10 Jul 1990

L19 ANSWER 357 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:246754 CAPLUS
DOCUMENT NUMBER: 118:246754
TITLE: Erythromycin: a **motilin receptor** agonist
AUTHOR(S): Shi, Xuanzheng; Zhang, Jingji
CORPORATE SOURCE: Dep. Physiol., Lanzhou Med. Coll., Lanzhou, 730000, Peop. Rep. China
SOURCE: Shengli Kexue Jinzhan (1990), 23(4), 365-7
CODEN: SLKHA8; ISSN: 0559-7765
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review, with 26 refs., of the pharmacol. of erythromycin as a **motilin receptor** agonist in the stomach.

L19 ANSWER 358 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1990:299048 BIOSIS
DOCUMENT NUMBER: PREV199039017229; BR39:17229
TITLE: ERYTHROMYCIN PROMOTES COLONIC TRANSIT IN HUMANS MEDIATION VIA **MOTILIN RECEPTORS.**
AUTHOR(S): HASLER W [Reprint author]; HELDSINGER A; SOUDAH H; OWYANG C
CORPORATE SOURCE: DEP INTERNAL MED, UNIV MICH, ANN ARBOR, MICH, USA
SOURCE: Gastroenterology, (1990) Vol. 98, No. 5 PART 2, pp. A358. Meeting Info.: 91ST ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION AND DIGESTIVE DISEASE WEEK, SAN ANTONIO, TEXAS, USA, MAY 12-18, 1990. GASTROENTEROLOGY. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Jun 1990
Last Updated on STN: 10 Jul 1990

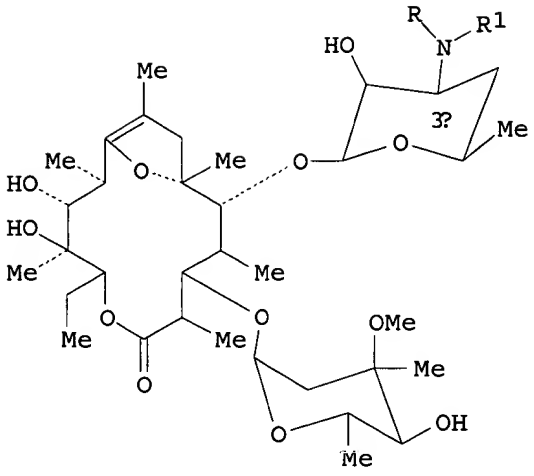
L19 ANSWER 359 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1990:298995 BIOSIS
DOCUMENT NUMBER: PREV199039017176; BR39:17176
TITLE: **MOTILIN RECEPTORS** IN THE COLON OF THE RABBIT.
AUTHOR(S): DEPOORTERE I [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LAB, GASTHUISBERG O AND N, LEUVEN, BELG
SOURCE: Gastroenterology, (1990) Vol. 98, No. 5 PART 2, pp. A345. Meeting Info.: 91ST ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION AND DIGESTIVE DISEASE WEEK, SAN ANTONIO, TEXAS, USA, MAY 12-18, 1990. GASTROENTEROLOGY. CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 27 Jun 1990
Last Updated on STN: 10 Jul 1990

L19 ANSWER 360 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:37997 BIOSIS

DOCUMENT NUMBER: PREV199140014977; BR40:14977
TITLE: ERYTHROMYCIN STIMULATES RECTOSIGMOID MOTILITY AND PROMOTES COLONIC TRANSIT IN HUMANS MEDIATION VIA NEURAL AND MYOGENIC **MOTILIN RECEPTORS.**
AUTHOR(S): HASLER W [Reprint author]; SOUDAH H; HELDSINGER A; LU Y; OWYANG C
CORPORATE SOURCE: DEP INTERNAL MED, UNIV MICH, ANN ARBOR, MICH, USA
SOURCE: Digestion, (1990) Vol. 46, No. SUPPL. 1, pp. 42.
Meeting Info.: 8TH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES, TIMMENDORFER STRAND/BALTIC SEA, WEST GERMANY, SEPTEMBER 4-8, 1990. DIGESTION.
CODEN: DIGEBW. ISSN: 0012-2823.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 5 Jan 1991
Last Updated on STN: 9 Jan 1991

L19 ANSWER 361 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1991:37941 BIOSIS
DOCUMENT NUMBER: PREV199140014921; BR40:14921
TITLE: THE **MOTILIN RECEPTOR** IS COUPLED TO A G-PROTEIN.
AUTHOR(S): DEPOORTERE I [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LAB, GASTHUISBERG O AND N, LEUVEN, BELGIUM
SOURCE: Digestion, (1990) Vol. 46, No. SUPPL. 1, pp. 22-23.
Meeting Info.: 8TH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES, TIMMENDORFER STRAND/BALTIC SEA, WEST GERMANY, SEPTEMBER 4-8, 1990. DIGESTION.
CODEN: DIGEBW. ISSN: 0012-2823.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 5 Jan 1991
Last Updated on STN: 9 Jan 1991

L19 ANSWER 362 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:459734 CAPLUS
DOCUMENT NUMBER: 113:59734
TITLE: Motilides, macrolides with gastrointestinal motor stimulating activity. I. O-Substituted and tertiary N-substituted derivatives of 8,9-anhydroerythromycin A 6,9-hemiacetal
AUTHOR(S): Tsuzuki, Kazuo; Sunazuka, Toshiaki; Marui, Shogo; Toyoda, Hajime; Omura, Satoshi; Inatomi, Nobuhiro; Itoh, Zen
CORPORATE SOURCE: Sch. Pharm. Sci., Kitasato Univ., Tokyo, 108, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1989), 37(10), 2687-700
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:59734
GI



I

AB Chemical modifications of 8,9-anhydroerythromycin A 6,9-hemiacetal (I; R = R1 = Me) which showed gastrointestinal motor stimulating (GMS) activity 10 times more potent than that of erythromycin A (EM-A), were undertaken to search for derivs. having stronger GMS activity and no antimicrobial activity; details are described in this and a subsequent paper. Displacement of a Me group of the dimethylamino group of I (R = R1 = Me) with an Et group and an iso-Pr group provided de(N-methyl)-N-ethyl-8,9-anhydroerythromycin A 6,9-hemiacetal (I; R = Me, R1 = Et) and de(N-methyl)-N-isopropyl-8,9-anhydroerythromycin A 6,9-hemiacetal (I; R = Me, R1 = CHMe2), resp. They showed significant GMS activity and no antibacterial activity. In particular, the GMS activity of I (R = Me, R1 = CHMe2) was increased to 248 times that of EM-A. EM-A and the derivs. obtained in this study mimic exogenous motilin in the dog. The name motilide, meaning a motilin-like macrolide, is proposed for this new family of macrolide compds.

L19 ANSWER 363 OF 391 MEDLINE on STN
ACCESSION NUMBER: 90040234 MEDLINE
DOCUMENT NUMBER: 90040234 PubMed ID: 2810120
TITLE: An erythromycin derivative, EM-523, induces motilin-like gastrointestinal motility in dogs.
AUTHOR: Inatomi N; Satoh H; Maki Y; Hashimoto N; Itoh Z; Omura S
CORPORATE SOURCE: Biology Research Laboratories, Takeda Chemical Industries, Osaka, Japan.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1989 Nov) 251 (2) 707-12.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19891221

AB The effect of an erythromycin derivative, EM-523, on gastrointestinal motility was investigated in conscious dogs and compared with that of motilin cisapride, trimebutine and metoclopramide. In the fasting state, EM-523 given i.v. or i.d. at 3 micrograms/kg or more induced contractions in the stomach that migrated along the small intestine. The pattern of the contractions was very similar to that induced by motilin. In the digestive state, EM-523 increased the amplitude of gastric contractions. Cisapride and metoclopramide increased gastrointestinal motility both in the fasting and digestive states; however, their contractile pattern was

different from that of EM-523. Trimebutine did not induce gastric motility in the fasting state but rather decreased gastric motility in the digestive state. The contractions induced by EM-523 and motilin were inhibited by atropine but were not affected by naloxone, suggesting that the cholinergic pathway is important in the exertion of their action. These results indicate that EM-523 mimics motilin in stimulating gastrointestinal motility and that this agent may be useful treat gastrointestinal disorders such as gastric stasis, gastroesophageal reflux, and postoperative ileus, and so forth.

L19 ANSWER 364 OF 391 MEDLINE on STN DUPLICATE 163
ACCESSION NUMBER: 89390631 MEDLINE
DOCUMENT NUMBER: 89390631 PubMed ID: 2782416
TITLE: Erythromycin is a **motilin receptor** agonist.
AUTHOR: Peeters T; Matthijs G; Depoortere I; Cachet T; Hoogmartens J; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, Katholieke Universiteit Leuven, Belgium.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1989 Sep) 257 (3 Pt 1) G470-4.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19891018

AB Erythromycin A (EMA) is a potent stimulator of gastrointestinal motor activity. In vitro studies suggest that it mimics motilin, a peptide that stimulates motor activity in human and in rabbit via smooth muscle receptors. We have compared the in vitro contractile effect of EMA and two derivatives, 8,9-anhydro-EMA-6,9-hemiketal (EM201) and EMA N-oxide, on rabbit duodenal smooth-muscle strips with their ability to displace iodinated motilin bound to crude smooth-muscle membrane fractions. The concentrations required to induce 50% of the maximum contractile response to a supramaximal dose of acetylcholine were 5.0 x 10(-8), 2.0 x 10(-6), and 1.0 x 10(-4) M for, respectively, EM201, EMA, and EMA N-oxide. The concentrations required to displace 50% of the labeled motilin were, in the same order, 1.0 x 10(-8), 1.3 x 10(-7), and 4.0 x 10(-6) M. Both parameters were well correlated. The dose-response curve of the EMA was parallel to that of motilin and the effects of motilin and EMA were additive. Contractions induced by EMA were insensitive to pretreatment with tetrodotoxin or atropine. EMA had no effect on muscle strips of rat or dog duodenum but did induce contractions in human strips. EMA was totally ineffective on ileal preparations, which are also unresponsive to motilin and in which motilin binding is absent. EMA has therefore the same regional and species specificity as motilin. We conclude that EMA is a **motilin receptor** agonist.

L19 ANSWER 365 OF 391 EMBASE on STN
ACCESSION NUMBER: 91001748 EMBASE
DOCUMENT NUMBER: 1991001748
TITLE: Structure-activity relation of erythromycin-related macrolides in inducing contractions and in displacing bound motilin in rabbit duodenum.
AUTHOR: Depoortere I.; Peeters T.L.; Matthijs G.; Cachet T.; Hoogmartens J.; Vantrappen G.
CORPORATE SOURCE: Gut Hormone Laboratory, Gasthuisberg O and N,B-3000 Leuven, Belgium
SOURCE: Journal of Gastrointestinal Motility, (1989) 1/2 (150-159).
ISSN: 1043-4518 CODEN: JGMOEB

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Erythromycin A appears to be a motilin agonist, although motilin (a peptide) and erythromycin A (a 14-member macrolide antibiotic carrying two sugar substituents) are structurally totally unrelated. To obtain information concerning the structural requirements for erythromycin's interaction with the **motilin receptor**, we studied 60 derivatives and seven fragments of erythromycin, and six macrolides with a 16-member ring structure. For every compound the ability to displace motilin bound to a crude homogenate of rabbit antral smooth muscle tissue and the ability to induce contractions in rabbit duodenal segments were determined. For both parameters dose-response curves were obtained, and the negative logarithms of the concentrations inhibiting 50% of the binding (pIC-50) or inducing 50% of the maximum response to a maximal contractile dose of acetylcholine (pEC-50) were determined. All macrolides with a 16-member ring structure were inactive in both types of experiments. In all erythromycin derivatives variations of the ring structure had a marked effect. For both parameters the order of potency was enol ether > pseudo-enol ether > parent ring > pseudo-hemiketal > anhydro. The two sugars attached to the ring were important too, because removing either or both of them resulted in an inactive compound. Modifications of the dimethylamino group of the desosamine sugar affect the potency, while the orientation of the cladinose moiety seems to be important too. For all active compounds, both parameters studied were well correlated ($r = 0.80$, $p < 0.001$). Our results support the concept that erythomycin-like macrolides are motilin agonists. The structural requirements of these 'motilides' involve the ring structure, especially the part that can be transformed into an enol ether, and both attached sugars. Potent derivatives may prove to be useful as gastrokinetic agents with a very specific target zone.

L19 ANSWER 366 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1989:348901 BIOSIS
DOCUMENT NUMBER: PREV198937039998; BR37:39998
TITLE: DEVELOPMENT OF **MOTILIN RECEPTORS** AND OF MOTILIN-INDUCED CONTRACTILITY IN RABBITS.
AUTHOR(S): DEPOORTERE I [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LAB, UNIV LEUVEN, LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1989) Vol. 96, No. 5 PART 2, pp. A119. Meeting Info.: 90TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, WASHINGTON, D.C., USA, MAY 13-19, 1989. GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 25 Jul 1989
Last Updated on STN: 29 Jul 1989

L19 ANSWER 367 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1989:348902 BIOSIS
DOCUMENT NUMBER: PREV198937039999; BR37:39999
TITLE: ERYTHROMYCIN MODULATES **MOTILIN RECEPTOR** DENSITY IN RABBIT.
AUTHOR(S): DEPOORTERE I [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LAB, UNIV LEUVEN, LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1989) Vol. 96, No. 5 PART 2, pp. A119. Meeting Info.: 90TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, WASHINGTON, D.C., USA, MAY 13-19, 1989. GASTROENTEROLOGY.

CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 25 Jul 1989
Last Updated on STN: 26 Aug 1989

L19 ANSWER 368 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 89234208 EMBASE
DOCUMENT NUMBER: 1989234208
TITLE: Erythromycin is a **motilin receptor** agonist.
AUTHOR: Peeters T.; Matthijs G.; Depoortere I.; Cachet T.; Hoogmartens J.; Vantrappen G.
CORPORATE SOURCE: Gult Hormone Laboratory, Department of Medical Research, Institute of Pharmaceutical Sciences, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (1989) 257/3 (20/3) (G470-G474).
ISSN: 0002-9513 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 002 Physiology
048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Erythromycin A (EMA) is a potent stimulator of gastrointestinal motor activity. In vitro studies suggest that it mimics motilin, a peptide that stimulates motor activity in human and in rabbit via smooth muscle receptors. We have compared the in vitro contractile effect of EMA and two derivatives, 8,9-anhydro-EMA-6,9-hemiketal (EM201) and EMA N-oxide, on rabbit duodenal smooth-muscle strips with their ability to displace iodinated motilin bound to crude smooth-muscle membrane fractions. The concentrations required to induce 50% of the maximum contractile response to a supramaximal dose of acetylcholine were 5.0 x 10-8, 2.0 x 10-6, and 1.0 x 10-7 M for, respectively, EM201, EMA, and EMA N-oxide. The concentrations required to displace 50% of the labeled motilin were, in the same order, 1.0 x 10-8, 1.3 x 10-7, and 4.0 x 10-6 M. Both parameters were well correlated. The dose-response curve of the EMA was parallel to that of motilin and the effects of motilin and EMA were additive. Contractions induced by EMA were insensitive to pretreatment with tetrodotoxin or atropine. EMA had no effect on muscle strips of rat or dog duodenum but did induce contractions in human strips. EMA was totally ineffective on ileal preparations, which are also unresponsive to motilin and in which motilin binding is absent. EMA has therefore the same regional and species specificity as motilin. We conclude that EMA is a **motilin receptor** agonist.

L19 ANSWER 369 OF 391 MEDLINE on STN DUPLICATE 164
ACCESSION NUMBER: 88134202 MEDLINE
DOCUMENT NUMBER: 88134202 PubMed ID: 3342053
TITLE: Erythromycin and its derivatives with motilin-like biological activities inhibit the specific binding of 125I-motilin to duodenal muscle.
COMMENT: Erratum in: Biochem Biophys Res Commun 1988 Mar 15;151(2):954
AUTHOR: Kondo Y; Torii K; Itoh Z; Omura S
CORPORATE SOURCE: Department of Physical Biochemistry, College of Medical Technology, Gunma University, Maebashi, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1988 Jan 29) 150 (2) 877-82.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880309

AB Erythromycin, one of the macrolide antibiotics, and its derivatives had been found to mimic actions of exogenous motilin, a gastrointestinal peptide hormone. We found that some of the macrolide compounds inhibited the specific binding of 125I-motilin to rabbit duodenum muscle at 15 C in a dose-dependent fashion. The inhibitory activity of several macrolides examined did not relate to their antibacterial activity but to their motilin-like activity. A 50% inhibition by EM536, a non-antibacterial erythromycin derivative with the highest motilin-like activity, was obtained at 3-40 nM and little higher than that of non-radioactive motilin (5-6 nM) under the present conditions. The results suggest that erythromycin and its derivatives mimic physiological actions of motilin by acting as agonists for a **motilin receptor.**

L19 ANSWER 370 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 165
ACCESSION NUMBER: 1988:366808 BIOSIS
DOCUMENT NUMBER: PREV198835051421; BR35:51421
TITLE: CHARACTERIZATION OF **MOTILIN RECEPTORS.**
AUTHOR(S): PEETERS T L [Reprint author]; BORMANS V; MATTHIJS G; VANTRAPPEN G
CORPORATE SOURCE: CENT GASTROENTEROLOGICAL RES, UNIV LEUVEN, B-3000 LEUVEN, BELGIUM
SOURCE: Gastroenterology, (1988) Vol. 94, No. 5 PART 2, pp. A347.
Meeting Info.: 89TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION, NEW ORLEANS, LOUISIANA, USA, MAY 14-20, 1988. GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 9 Aug 1988
Last Updated on STN: 9 Aug 1988

L19 ANSWER 371 OF 391 MEDLINE on STN DUPLICATE 166
ACCESSION NUMBER: 88161362 MEDLINE
DOCUMENT NUMBER: 88161362 PubMed ID: 3348375
TITLE: **Motilin receptors** on isolated gastric smooth muscle cells.
AUTHOR: Louie D S; Owyang C
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1988 Feb) 254 (2 Pt 1) G210-6.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198804
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880411

AB Motilin has a stimulating effect on gastrointestinal motility. The mechanism of its action is not known. Direct and neuronal effects have been postulated. To determine if receptors are present on smooth muscle cells we investigated the effect of synthetic porcine motilin and its interaction with acetylcholine on isolated guinea pig gastric smooth muscle cells. Motilin elicited a dose-dependent contraction of gastric

smooth muscle cells. Minimal (8.3 +/- 1.3%) and maximal (33.9 +/- 2.4%) responses were observed at 10(-12) and 10(-6) M, respectively. The ED50 of motilin was 10(-9) M. Acetylcholine also elicited a dose-response muscle contraction with a maximal response observed at 10(-7) M. Atropine (10(-7) M) completely inhibited the maximal response to acetylcholine but did not have any effect on the contractile response to motilin. In addition, dibutyryl guanosine 3',5'-cyclic monophosphate (10(-3) M) and substance P antagonist, spantide (10(-4) M), also did not inhibit the action of motilin. Acetylcholine (10(-11) M) shifted the dose-response curve of motilin to the left by 1.5 log units. The maximal response to the combination of motilin (10(-6) M) and acetylcholine (10(-11) M) was 32 +/- 3.2%, which was similar to the maximal response to motilin alone. It is concluded that distinct motilin and muscarinic receptors are present on guinea pig gastric smooth muscle cells. The interaction between motilin and acetylcholine is additive and not potentiative.

L19 ANSWER 372 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 88:503663 SCISEARCH
THE GENUINE ARTICLE: P9465
TITLE: MACROLIDE ANTIBIOTICS ARE **MOTILIN RECEPTOR** AGONISTS
AUTHOR: DEPOORTERE I (Reprint); PEETERS T L; MATTHIJS G; VANTRAPPEN G
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, CTR GASTROENTEROL RES, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: HEPATO-GASTROENTEROLOGY, (1988) Vol. 35, No. 4, pp. 198.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 373 OF 391 MEDLINE on STN DUPLICATE 167
ACCESSION NUMBER: 89161210 MEDLINE
DOCUMENT NUMBER: 89161210 PubMed ID: 3231745
TITLE: Comparison of motilin binding to crude homogenates of human and canine gastrointestinal smooth muscle tissue.
AUTHOR: Peeters T L; Bormans V; Vantrappen G
CORPORATE SOURCE: Department of Medical Research, University of Leuven, Belgium.
SOURCE: REGULATORY PEPTIDES, (1988 Nov) 23 (2) 171-82.
Journal code: 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198904
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890411

AB Pharmacological studies indicate that in man and in rabbit, but not in dog, motilin has a direct influence upon gastrointestinal smooth muscle. In accordance with this hypothesis we have presented direct biochemical evidence for the presence of **motilin receptors** on rabbit smooth muscle tissue. We have now extended our studies to human and canine tissue. Tissue homogenates were studied in binding experiments with iodinated porcine [Leu13]motilin and iodinated canine motilin. It was ascertained that the iodination procedure had little effect on the biological activity of the porcine analogue. In the human antrum specific binding of the iodinated porcine analogue was only found in the smooth muscle layer. It was absent in mucosal or serosal preparations. At 30 degrees C and pH 8.0, binding was maximal after 60 min of incubation, and was reversed by the addition of unlabeled porcine motilin. Binding was enhanced in the presence of calcium and magnesium ions. At a concentration of 10 mM MgCl2, binding was 220% of the binding observed in

its absence. Displacement studies with synthetic porcine [Leu13]motilin or synthetic natural porcine motilin indicated a dissociation constant (Kd) of 3.6 +/- 1.6 nM and a maximal binding capacity (Bmax) of 77 +/- 9 fmol per mg protein. Canine motilin displaced iodinated porcine motilin with an apparent Kd of 2.2 +/- 0.9 nM. Compared to antral binding, receptor density decreased aborally and orally, and was absent in jejunum and ileum. In dog specific binding could not be demonstrated in antral and duodenal tissue, neither with labeled porcine nor with labeled canine motilin. However, labeled canine motilin was equipotent to labeled porcine motilin in binding studies with human tissue: the dissociation constant was 0.9 +/- 0.6 nM. The present studies therefore demonstrate the existence of a specific **motilin receptor** in the antroduodenal region of the human gut. Apparently, such receptors are not present in the canine gut. Our data support the hypothesis that in the human gastrointestinal tract, the gastroduodenal area is motilin's target region.

L19 ANSWER 374 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1989:153237 BIOSIS
DOCUMENT NUMBER: PREV198936075278; BR36:75278
TITLE: ERYTHROMYCIN AND ITS DERIVATIVES ARE **MOTILIN RECEPTOR** AGONISTS.
AUTHOR(S): PEETERS T L [Reprint author]; MATTHIJS G; DEPOORTERE I; CACHET T; HOOGMARTENS J; VANTRAPPEN G
CORPORATE SOURCE: LEUVEN, BELGIUM
SOURCE: Biomedical Research (Tokyo), (1988) Vol. 9, No. SUPPL. 1, pp. 95.
Meeting Info.: SEVENTH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES, SHIZUOKA, JAPAN, NOVEMBER 1-4, 1988. BIOMED RES.
CODEN: BRESD5. ISSN: 0388-6107.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 13 Mar 1989
Last Updated on STN: 13 Mar 1989

L19 ANSWER 375 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1989:153182 BIOSIS
DOCUMENT NUMBER: PREV198936075223; BR36:75223
TITLE: FURTHER CHARACTERIZATION OF **MOTILIN RECEPTORS.**
AUTHOR(S): PEETERS T L [Reprint author]; BORMANS V; MATTHIJS G; VANTRAPPEN G
CORPORATE SOURCE: LEUVEN, BELGIUM
SOURCE: Biomedical Research (Tokyo), (1988) Vol. 9, No. SUPPL. 1, pp. 66.
Meeting Info.: SEVENTH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES, SHIZUOKA, JAPAN, NOVEMBER 1-4, 1988. BIOMED RES.
CODEN: BRESD5. ISSN: 0388-6107.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 13 Mar 1989
Last Updated on STN: 13 Mar 1989

L19 ANSWER 376 OF 391 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 88077262 EMBASE
DOCUMENT NUMBER: 1988077262
TITLE: **Motilin receptors** on isolated gastric smooth muscle cells.
AUTHOR: Louie D.S.; Owyang C.
CORPORATE SOURCE: Department of Internal Medicine, Gastroenterology Research

Unit, The University of Michigan Medical Center, Ann Arbor, MI 48109, United States
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (1988) 254/2 (17/2) (G210-G216).
ISSN: 0002-9513 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 002 Physiology
027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Motilin has a stimulating effect on gastrointestinal motility. The mechanism of its action is not known. Direct and neuronal effects have been postulated. To determine if receptors are present on smooth muscle cells we investigated the effect of synthetic porcine motilin and its interaction with acetylcholine on isolated guinea pig gastric smooth muscle cells. Motilin elicited a dose-dependent contraction of gastric smooth muscle cells. Minimal (8.3 ± 1.3%) and maximal (33.9 ± 2.4%) responses were observed at 10-12 and 10-6 M, respectively. The ED50 of motilin was 10-9 M. Acetylcholine also elicited a dose-response muscle contraction with a maximal response observed at 10-7 M. Atropine (10-7 M) completely inhibited the maximal response to acetylcholine but did not have any effect on the contractile response to motilin. In addition, dibutyryl guanosine 3',5'-cyclic monophosphate (10-3 M) and substance P antagonist, spantide (10-4 M), also did not inhibit the action of motilin. Acetylcholine (10-11 M) shifted the dose-response curve of motilin to the left by 1.5 log units. The maximal response to the combination of motilin (10-6 M) and acetylcholine (10-11 M) was 32 ± 3.2%, which was similar to the maximal response to motilin alone. It is concluded that distinct motilin and muscarinic receptors are present on guinea pig gastric smooth muscle cells. The interaction between motilin and acetylcholine is additive and not potentiative.

L19 ANSWER 377 OF 391 MEDLINE on STN DUPLICATE 168
ACCESSION NUMBER: 87134844 MEDLINE
DOCUMENT NUMBER: 87134844 PubMed ID: 3817389
TITLE: Comparative stimulation of motilin duodenal receptor by porcine or canine motilin.
AUTHOR: Poitras P; Lahaie R G; St-Pierre S; Trudel L
SOURCE: GASTROENTEROLOGY, (1987 Mar) 92 (3) 658-62.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198703
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19900303
Entered Medline: 19870330
AB Motilins purified from porcine and canine intestine differ in their amino acid composition in positions 7-8-12-13-14. We studied in vitro the contractile response of longitudinal duodenal muscles from various animals (guinea pig, rabbit, dog) to porcine and canine synthetic motilins. Both substances failed to elicit contraction of the guinea pig duodenum but were active and equally potent on rabbit muscle. In dogs, porcine motilin was inactive at the concentrations tested (up to 10(-4) M) whereas canine motilin induced duodenal contractions in a dose-response fashion (mean dose required to induce half-maximal response: 4.82 +/- 0.25 X 10(-5) M). The contraction generated by synthetic canine motilin (10(-5) M) was not influenced by atropine, hexamethonium, tetrodotoxin, naloxone, or sodium nitroprusside (all used at 10(-4) M) but was blocked by verapamil

(10(-4)). Our study shows that species-related structural alterations in motilin molecules generate different bioactive capacities in some animal species, suggests that the middle portion of the molecule is important for its bioactive expression, suggests the presence of **motilin receptors** on canine duodenal muscle, and suggests that an influx of extracellular calcium is involved in the canine duodenal muscle contraction elicited by canine motilin.

L19 ANSWER 378 OF 391 MEDLINE on STN DUPLICATE 169
ACCESSION NUMBER: 87093153 MEDLINE
DOCUMENT NUMBER: 87093153 PubMed ID: 3797704
TITLE: Comparison of the biological activity of canine and porcine motilin in rabbit.
AUTHOR: Peeters T L; Bormans V; Matthijs G; Vantrappen G
SOURCE: REGULATORY PEPTIDES, (1986 Nov) 15 (4) 333-9.
Journal code: 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198702
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19870211

AB The biological activity of porcine and canine motilin was studied in rabbits by establishing dose-response curves of both peptides using two different methods. The dissociation constant, obtained from the displacement of iodinated porcine motilin by canine motilin was 0.6 +/- 0.3 nM, versus 1.2 +/- 0.4 nM for porcine motilin. For the 13-norleucine and 13-leucine analogues of porcine motilin a value of 0.8 +/- 0.3 nM was obtained. Both motilins were almost equipotent in stimulating the in vitro contractile response of longitudinal smooth muscle strips: half-maximal effect was achieved at a concentration of 1.0 +/- 0.1 nM for canine versus 1.3 +/- 0.2 nM for the 13-norleucine analogue of porcine motilin. We conclude that porcine and canine motilin have a comparable bioactivity in the rabbit, although canine motilin is slightly more effective. The **motilin receptor** is probably specific for the N-terminal portion which is identical in both molecules.

L19 ANSWER 379 OF 391 MEDLINE on STN DUPLICATE 170
ACCESSION NUMBER: 87068727 MEDLINE
DOCUMENT NUMBER: 87068727 PubMed ID: 3786836
TITLE: **Motilin receptors** in rabbit stomach and small intestine.
AUTHOR: Bormans V; Peeters T L; Vantrappen G
SOURCE: REGULATORY PEPTIDES, (1986 Sep) 15 (2) 143-53.
Journal code: 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19970203
Entered Medline: 19870105

AB **Motilin receptors** in rabbit antral and duodenal smooth muscle tissue were characterized by direct binding technique using 125I-labeled porcine motilin as a tracer ligand. Binding at 30 degrees C was maximal at 90 min, was saturable and partially reversible. Displacement studies with natural porcine motilin, synthetic leucine-motilin or norleucine-motilin indicated a dissociation constant (Kd) of 1.1 +/- 0.3 nM and a maximal binding capacity (Bmax) of 42 +/- 10 fmol/mg protein. Binding was unaffected by glucagon, pancreatic polypeptide and somatostatin, but substance P interfered via an unknown mechanism. By density gradient centrifugation **motilin**

receptors were shown to be present in plasma membranes. Binding could only be demonstrated in preparations from antrum and upper duodenum. These observations provide evidence for a localized target region for motilin in the gastrointestinal tract, and for a direct interaction of motilin with gastrointestinal smooth muscle tissue.

L19 ANSWER 380 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 86:543500 SCISEARCH
THE GENUINE ARTICLE: E1393
TITLE: **MOTILIN RECEPTORS** IN RABBIT STOMACH AND SMALL-INTESTINE
AUTHOR: BORMANS V (Reprint); PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, DEPT MED RES, CTR GASTROENTEROL RES, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: REGULATORY PEPTIDES, (1986) Vol. 15, No. 2, pp. 143-153.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 20

L19 ANSWER 381 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:28056 CAPLUS
DOCUMENT NUMBER: 106:28056
TITLE: Mechanism of action of motilin in mediating fasting motor activity
AUTHOR(S): Sarr, Michael G.; Duenes, Judith A.; Tanaka, M.
CORPORATE SOURCE: Dep. Surg., Mayo Med. Sch., Rochester, MN, 55905, USA
SOURCE: Surgical Forum (1986), 37, 136-9
CODEN: SUFOAX; ISSN: 0071-8041
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The dose of motilin [52906-92-0] required to induce a premature migrating motor complex in the duodenum of dogs was the same whether given close intra-arterially, and thus directly into the blood supply to the proximal duodenum, or i.v., and thus mixed in the vascular volume Evidently, receptors for motilin are not located in the proximal duodenal wall. Moreover, humoral initiation of fasting motor activity in the duodenum apparently does not occur by induction of an independent initiation mechanism located within the bowel wall itself.

L19 ANSWER 382 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1987:16081 BIOSIS
DOCUMENT NUMBER: PREV198732006214; BR32:6214
TITLE: COMPARED BIOACTIVITIES OF PORCINE AND CANINE SYNTHETIC MOTILINS ON DUODENAL CONTRACTION IN-VITRO DEMONSTRATION OF **MOTILIN RECEPTORS** ON CANINE DUODENAL MUSCLES.
AUTHOR(S): POITRAS P [Reprint author]; TRUDEL L; LAHAIE R G; SAINT PIERRE S
CORPORATE SOURCE: CLIN RES CENT, HOPITAL SAINT-LUC, UNIV MONTREAL, QUE, CAN
SOURCE: Canadian Journal of Physiology and Pharmacology, (1986) No. JULY, pp. 100.
Meeting Info.: SIXTH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES, VANCOUVER, B.C., CANADA, JULY 6-10, 1986. CAN J PHYSIOL PHARMACOL.
CODEN: CJPPA3. ISSN: 0008-4212.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 9 Dec 1986
Last Updated on STN: 9 Dec 1986

L19 ANSWER 383 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 171

ACCESSION NUMBER: 1985:219737 BIOSIS
DOCUMENT NUMBER: PREV198529109733; BR29:109733
TITLE: REGIONAL AND TEMPORAL VARIATIONS OF **MOTILIN RECEPTOR** DENSITY IN THE HUMAN AND RABBIT GASTROINTESTINAL TRACT.
AUTHOR(S): PEETERS T L [Reprint author]; BORMANS V; VANTRAPPEN G
CORPORATE SOURCE: CENT GASTROENTEROL RES, UNIV LEUVEN, B-3000 LEUVEN, BELGIUM
SOURCE: Digestive Diseases and Sciences, (1985) Vol. 30, No. 8, pp. 787.
Meeting Info.: 10TH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL MOTILITY, ROCHESTER, MINN., USA, SEPT. 8-11, 1985. DIG DIS SCI.
CODEN: DDSCDJ. ISSN: 0163-2116.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH

L19 ANSWER 384 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1985:71819 BIOSIS
DOCUMENT NUMBER: PREV198528071819; BR28:71819
TITLE: CHARACTERIZATION OF **MOTILIN RECEPTORS** IN RABBIT ANTRAL SMOOTH MUSCLE TISSUE.
AUTHOR(S): BORMANS V [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LABORATORY, KATHOLIEKE UNIVERSITEIT TE LEUVEN, LEUVEN, BELGIUM
SOURCE: Gut, (1984) Vol. 25, No. 11, pp. A1315.
Meeting Info.: 2ND EUROPEAN SYMPOSIUM ON GASTROINTESTINAL MOTILITY, OXFORD, ENGLAND, SEPT. 5-7, 1984. GUT.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH

L19 ANSWER 385 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 84:597176 SCISEARCH
THE GENUINE ARTICLE: TS139
TITLE: CHARACTERIZATION OF **MOTILIN RECEPTORS** IN RABBIT ANTRAL SMOOTH-MUSCLE TISSUE
AUTHOR: BORMANS V (Reprint); PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: CATHOLIC UNIV LEUVEN, GUT HORMONE LAB, B-3000 LOUVAIN, BELGIUM
COUNTRY OF AUTHOR: BELGIUM
SOURCE: GUT, (1984) Vol. 25, No. 11, pp. 1315.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 386 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1984:133746 BIOSIS
DOCUMENT NUMBER: PREV198427050238; BR27:50238
TITLE: **MOTILIN RECEPTORS** ON ISOLATED GASTRIC SMOOTH MUSCLE CELLS INTERACTION WITH ACETYL CHOLINE.
AUTHOR(S): LOUIE D [Reprint author]; OWYANG C
CORPORATE SOURCE: DEPARTMENT OF INTERNAL MEDICINE, GASTROENTEROLOGY RESEARCH UNIT, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH 48109, USA
SOURCE: Gastroenterology, (1984) Vol. 86, No. 5 PART 2, pp. 1167.
Meeting Info.: THE 85TH ANNUAL MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION HELD IN CONJUNCTION WITH THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASE, AND THE GASTROENTEROLOGY STUDY GROUP, NEW ORLEANS, LA., USA, MAY 19-25, 1984. GASTROENTEROLOGY.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR

LANGUAGE: ENGLISH

L19 ANSWER 387 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 84:214535 SCISEARCH
THE GENUINE ARTICLE: SM831
TITLE: **MOTILIN RECEPTORS** ON ISOLATED GASTRIC SMOOTH-MUSCLE CELLS - INTERACTION WITH ACETYLCHOLINE
AUTHOR: LOUIE D (Reprint); OWYANG C
CORPORATE SOURCE: UNIV MICHIGAN, DEPT INTERNAL MED, GASTROENTEROL RES UNIT, ANN ARBOR, MI, 48109
COUNTRY OF AUTHOR: USA
SOURCE: GASTROENTEROLOGY, (1984) Vol. 86, No. 5, pp. 1167.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 388 OF 391 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1985:22703 BIOSIS
DOCUMENT NUMBER: PREV198528022703; BR28:22703
TITLE: DEMONSTRATION AND CHARACTERIZATION OF **MOTILIN RECEPTORS** IN RABBIT INTESTINAL SMOOTH MUSCLE TISSUE.
AUTHOR(S): BORMANS V [Reprint author]; PEETERS T L; VANTRAPPEN G
CORPORATE SOURCE: GUT HORMONE LAB, CENT GASTROENTEROL RES, GASTHUISBERG O N, B-3000 LEUVEN, BELGIUM
SOURCE: Digestive Diseases and Sciences, (1984) Vol. 29, No. 8 SUPPL, pp. 12S.
Meeting Info.: 5TH INTERNATIONAL SYMPOSIUM ON GASTROINTESTINAL HORMONES, ROCHESTER, MINN., USA, SEPT. 30-OCT. 3, 1984. DIG DIS SCI.
CODEN: DDSCDJ. ISSN: 0163-2116.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH

L19 ANSWER 389 OF 391 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 83:155402 SCISEARCH
THE GENUINE ARTICLE: QH771
TITLE: SMOOTH-MUSCLE **MOTILIN RECEPTORS** IN RABBIT STOMACH AND DUODENUM
AUTHOR: BORMANS V (Reprint); PEETERS T L; VANTRAPPEN G R
SOURCE: GUT, (1983) Vol. 24, No. 4, pp. A355.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: No References

L19 ANSWER 390 OF 391 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1975:558536 CAPLUS
DOCUMENT NUMBER: 83:158536
TITLE: Analysis of the motor effects of 13-norleucine motilin on the rabbit, guinea pig, rat, and human alimentary tract in vitro
AUTHOR(S): Strunz, Ulrich; Domschke, Wolfram; Mitznegg, Peter; Domschke, Sigurd; Schubert, Ernst; Wuensch, Erich; Jaeger, Ernst; Demling, Ludwig
CORPORATE SOURCE: Dep. Med., Univ. Erlangen-Nuernberg, Erlangen, Fed. Rep. Ger.
SOURCE: Gastroenterology (1975), 68(6), 1485-91
CODEN: GASTAB; ISSN: 0016-5085
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Guinea pig and rat alimentary tract prepns. were refractory to 13-norleucine motilin (I) [55524-56-6] action, muscle strips of the

stomach and upper small intestine from rabbit and man were highly sensitive to I, contractile responses elicited with concns. less than 2 + 10-9M. Although circular muscle from rabbit colon responded to I, Taenia coli prepns. were unaffected by the polypeptide. In man the reverse was observed Gallbladder, uterine, and vascular smooth muscle were unresponsive to I. Pharmacol. anal. showed that the effects of I on the gastrointestinal muscle were not mediated via nervous pathways. Ganglion blockade by hexamethonium iodide [870-62-2], block of axonal conduction by tetrodotoxin [4368-28-9], or anticholinergic action by atropine sulfate [55-48-1] did not affect I reaction. I apparently caused contractions by stimulating receptors on or in the muscle cell. By use of pheniramine [86-21-5], histamine receptors could be differentiated from the site of I action. As the contractile response to I was abolished by verapamil [52-53-9], a role for I in the transport of Ca2+ to the cytosol of intestinal smooth muscle might by considered.

L19 ANSWER 391 OF 391 JAPIO (C) 2004 JPO on STN
ACCESSION NUMBER: 2000-044595 JAPIO
TITLE: PHENETHYLAMINE DERIVATIVE
INVENTOR: KOTAKE KENICHIRO; KOZONO TOSHIRO; SATO TSUTOMU; TAKANASHI HISANORI
PATENT ASSIGNEE(S): CHUGAI PHARMACEUT CO LTD
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000044595	A	20000215	Heisei	C07K005-083

APPLICATION INFORMATION
STN FORMAT: JP 1998-229586 19980814
ORIGINAL: JP10229586 Heisei
PRIORITY APPLN. INFO.: JP 1997-255879 19970815
PRIORITY APPLN. INFO.: JP 1998-186802 19980528
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined Applications, Vol. 2000
AN 2000-044595 JAPIO
AB PROBLEM TO BE SOLVED: To obtain a specific new phenethylamine derivative exhibiting **motilin receptor** antagonism and therefore useful as a medicament effective in improving diseases with raised blood motilin levels such as hypersensitive colon syndrome.
SOLUTION: This new phenethylamine derivative is shown by formula I [A is an (N α-substituted) amino acid residue; R1 is a group of the formula R6-CO (R6 is an alkyl, an alkenyl, aromatic ring or the like), (substituted) 2-7C alkyl or the like; R2 is H, a (substituted) 1-3C alkyl; R3 is a group of the formula CO-R7 (R7 is H, a 1-5C alkyl, 3-7C cycloalkyl or the like), (substituted) 1-5C alkyl or the like; R4 is H, a 1-6C alkyl or group of formula II (R15 is H or methyl; R16 and R17 are joined together to form a 3-7C cycloalkyl or the like); R5 is H or a group of the formula OR8 (R8 is H or a 1-4C alkyl)], exhibiting **motilin receptor** antagonism, therefore being useful in treating e.g. hypersensitive colon syndrome. This new compound of formula I is obtained, for example, by direct condensation reaction of an α-amino group-protected substituted phenylalanine ester with an amine.

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 23:08:26 ON 08 FEB 2004